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NOTE

Synthesis and Antifungal Activity of 3,5-Disubstituted Phenyl Imino-1,2,4-Triazoles

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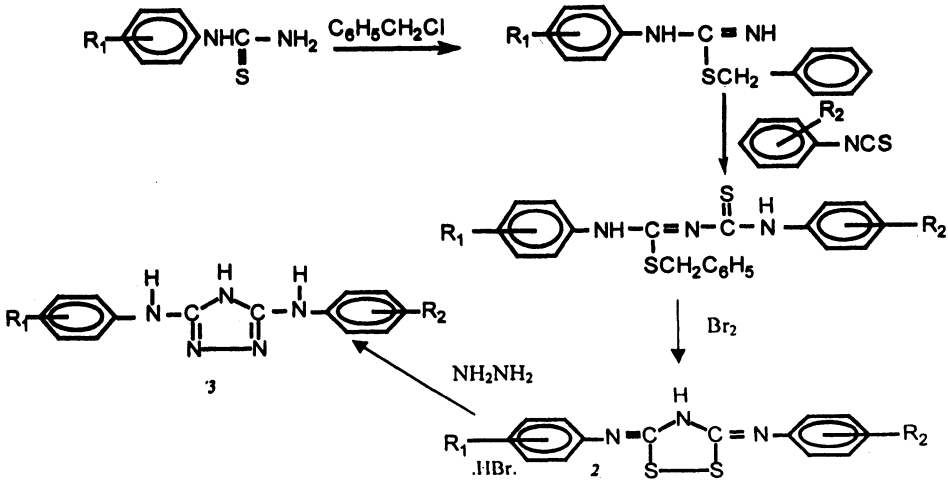
A series of new triazoles have been synthesised and evaluated for antifungal activity against *Candida albicans.*

Key Words: Antifungal activity, 3,5-Disubstituted phenyl imino-1,2,4-triazoles.

1,2,4-Triazole nucleus is associated with diverse pharmacological properties like analgesic, antiasthmatic, diuretic, antihypertensive, anticholinergic, antibacterial, antifungal and antinflammatory activities.[1-4]

Many triazoles have been clinically used as antifungal drugs or running under clinical trial for getting antifungal drugs.[5,6] Efforts are still continuing to get the suitable antifungal agent to overcome the resistance developed towards common chemotherapeutic agent specially in AIDS and liver disease. In this paper, a series of triazoles are synthesized and evaluated for antifungal activity.

Synthesis of 1,2,4-triazoles is carried out in two steps (Scheme-1) (General Procedure).



Scheme-1

Step-1: Synthesis of 3,5-disubstituted phenylimino 1,2,4-dithiazolidine hydrobromide (2): Phenyl thiourea/substituted phenyl thiourea and benzyl chloride are refluxed in ethanol for 1 h. The ethanol is evaporated to get solid residue which is extracted with benzene after basification with ammonia solution. The extract is dried over anhydrous calcium chloride and then evaporated to get 1-phenyl-2-S-benzyl isothiourea as viscous liquid. The viscous liquid is refluxed with phenyl/substituted phenyl isothiocyanate in benzene for 3 h. The solvent is distilled out to get a semisolid mass which is washed with petroleum ether. The solid mass is converted into a thin paste in chloroform and bromine solution is added dropwise with constant stirring till the reaction mixture turns yellowish brown. The solid mass thus separated is crystallised with alcohol to yield respective 3,5-disubstituted phenylimino-1,2-4-dithiazolidine hydrobromide. IR (KBr) 3300 ν(NH), 1530 cm^{-1} ν(S—C—N); ^1H NMR (DMSO-d_6); δ 6.65 (m, 1H, NH), 7.2–7.6 (m, Ar—H).

Step II: Synthesis of 3,5-disubstituted phenylimino 1,2,4-triazole (3): The above 1,2,4-dithiazolidine derivatives are refluxed with hydrazine hydrate in ethanol for 3 h. The contents are concentrated and then cooled down to get respective 3,5-disubstituted phenylimino-1,2,4-triazoles (Table-1). IR (KBr) 3300 cm^{-1} ν(NH), ^1H NMR (DMSO-d_6) δ 4.05 (s, 2H, NH).

TABLE-1
ANTIFUNGAL ACTIVITY OF 3,5-DISUBSTITUTED PHENYL IMINO 1,2,4-TRIAZOLES

Compound	R_1	R_2	m.f.	m.p. (°C)	Zone of inhibition (mm)
3a	H	H	$C_{14}H_{13}N_5$	226	10
3b	H	*p*-Cl	$C_{14}H_{12}N_5Cl$	242	14
3c	H	*p*-Br	$C_{14}H_{12}N_5Br$	115	16
3d	H	*o*-CH_3	$C_{15}H_{15}N_5$	118	6
3e	*o*-CH_3	H	$C_{15}H_{15}N_5$	122	10
3f	*o*-CH_3	Cl	$C_{15}H_{14}N_5Cl$	218	16
3g	*o*-CH_3	Br	$C_{15}H_{14}N_5Br$	220	13.2
3h	*o*-CH_3	*o*-CH_3	$C_{16}H_{17}N_5$	128	16
3i	*p*-Cl	H	$C_{14}H_{12}N_5Cl$	154	14
3j	*p*-Cl	*p*-Cl	$C_{14}H_{11}N_5Cl_2$	224	15
3k	*p*-Cl	*p*-Br	$C_{14}H_{11}N_5BrCl$	228	16
3l	*p*-Cl	*o*-CH_3	$C_{15}H_{14}N_5Cl$	120	10.6
3m	*p*-Br	H	$C_{14}H_{12}N_5Br$	154	12.2
3n	*p*-Br	*p*-Cl	$C_{14}H_{11}N_5BrCl$	240	15.4
3o	*p*-Br	*p*-Br	$C_{15}H_{11}N_5Br_2$	240	10.8
3p	*p*-Br	*o*-CH_3	$C_{15}H_{14}N_5Br$	120	11.8
Fluconazole					17

Concentration of standard drug and test compound used = 100 μg/mL.

Antifungal activity: It is carried out by cup-plate method by using blood agar media and zone of inhibition (mm) is compared with standard drug fluconazole (Table-1).

Conclusion

The above triazoles have been found to show appreciable antifungal activity against *Candida albicans* quite comparable to fluconazole. The results show that the presence of para-chlorophenyl at 3 or 5 positions or at both the positions increases the antifungal activity.

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