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THEORY OF SOME PYRIDINE DERIVATIVES AS POTENT ANTIFUNGAL AGENTS

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ABSTRACT
A series of 2-aminomethylene[2'-(3"-chloro-2"-oxo-4"-substitutedaryl-1"-azetidinyl)-1',3',4'-thiaziazol-5'-yl]pyridine (5a-5d) and 2-aminomethylene[2'-(2"-substitutedaryl-4"-thiazolidinonon-3"-yl)-1',3',4'-thiadiazol-5'-yl]pyridine (6a-6d) have been synthesized from 2-aminomethylene(2'-substituted arylidene imino-1',3',4'-thiadiazol-5'-yl)pyridine (4a-4d) by cycloaddition reaction of chloroacetylchloride and thioglycolic acid respectively. All the compounds were screened for their antifungal activity. Compound 6b was found to be the most potent compound of the series and its activity was compared with the reference drugs Fluconazole and Gieseofulvin. The structures of these compounds have been established by IR, ^{1}HNMR and mass spectroscopic data.

INTRODUCTION
Research in the field of pyridine derivatives has yielded a number of clinically useful antifungal drugs. Pyridine derivatives of different heterocyclic nucleus have shown potent pharmacological properties like antifungal[1-3], antitubercular[4], antibacterial[5], antimicrobial[6], insecticidal[7] etc. Furthermore, different congeners of thiadiazole[8-9], thiazolidinone[10-11], and azetidinone[12-13] have also been reported to exhibit potent antifungal activities by several scientists. In the light of these observations compounds of series I were synthesized incorporating thiadiazole, thiazolidinone, and azetidinone moieties at 2-position of pyridine nucleus with a hope to develop better antifungal agents. These compounds have been screened for their antifungal activity.

The synthetic routes of compounds are outlined in Scheme I. As shown in Scheme I compound 1 i.e 2 ethylaminopyridinoacetate was formed by the reaction of starting materal i.e 2-aminopyridine with ethylchloroacetate and anhydrous K_2CO_3, which further reacted with thiosemicarbazide to give 2-aminopyridineacetylthiosemicarbaide (compound 2). Compound 2 when treated with conc. H_2SO_4 and then neutralized with liquid ammonia resulted in the formation of compound 3 i.e 2-aminomethylene-(2´-amino-1´,3´,4´-thiadiazol-5´-yl)pyridine, which when treated with different substituted aromatic aldehydes formed various substituted arylidine derivatives (4a-4d). These arylidine derivatives on treatment with triethylamine and chloroacetylchloride yielded different azetidinyl derivatives i.e compound 5a-5d. On the other hand these arylidine derivatives on reaction with thioglycolic acid and anhydrous $ZnCl_2$ furnished various thiazolidinone derivatives i.e compound 6a-6d.

IR spectrum of compound 1 exhibited various characteristic bands of NH at ν 3272.33, CH_2 at ν 2845.33, C=O at ν 1740.025. Its ^{1}HNMR spectrum displayed a sharp singlet at δ 9.60 for one proton of N<u>H</u>C<u>H</u>$_2$, exchangeable with D_2O, a doublet at δ 4.40 for two protons of NHC<u>H</u>$_2$, a quadret at δ 4.20 for two protons of COOC<u>H</u>$_2$CH$_3$, a triplet at δ 1.25 for three protons of COOCH$_2$C<u>H</u>$_3$. The signals of different protons of pyridine nucleus appeared at δ 8.35 (doublet), δ 7.60 (doublet doublet), δ 7.40 (doublet) and δ 7.30 (doublet doublet) (m/z 180). The structure of compound 2 was established on the basis of the changes observed in IR and ^{1}HNMR spectra of the compound as compared to its parent compound i.e. compound 1. The changes are : appearance of band of C=S at ν 1180.76 and disappearance of band at ν 1740.02 due to C=O in its IR spectrum, and further in its ^{1}HNMR spectrum, presence of a multiplet at δ 8.80 due to 4 protons of N<u>H</u>N<u>H</u>CSN<u>H</u>$_2$.

The structure of compound 3 is established by its IR and ^{1}HNMR spectrum. Appearance of peaks at ν 684.27, ν 1277.44 for C–S–C and N–N respectively and disappearance of absorption bands due to C=S is

its IR spectrum confirms the formation of thiadiazole ring. Further in its ^{1}HNMR spectrum disappearance of multiplet of NHNHCSNH_2 and presence of a singlet at δ 8.20 due to two protons of NH_2, helps in establishing its structure.

Fundamental bands of OH, NH, C=N, C=C of aromatic ring, N–N, CH_2, C–S–C group were observed in IR spectrum of compound 4b at ν 3320.89, ν 3343.52, ν 1592.44, ν 1510.27, ν 1272.51, ν 2850.52, ν 680.25 respectively. Presence of sharp singlet at δ 12.40 for one proton of OH group, exchangeable with D_2O, appearance of a sharp singlet at δ 8.40 due to a proton of N=CH–Ar, and that of a multiplate at 7.15-7.50 due to four aromatic protons in its ^{1}HNMR spectrum confirmed the formation 4b, and molecular ion peak at m/z 311 was also observed in its mass spectrum.
In ^{1}HNMR spectrum of 5b, disappearance of sharp signlet at δ 8.40 due to N=CH–Ar, appearance of doublet at δ 5.05 for one proton of CHCl and a doublet at δ 4.75 for N–CH–Ar where as in its I R appearance of fundamental band of C=O of β-lactam at ν 1725.36, indicated the formation of azetidinone ring.
In compound 6b appearance of absorption band of C=O of β thialactam at ν 1665.83 in IR and that of a singlet of CH–Ar at δ 6.18 in ^{1}HNMR of compound 6b supported the synthesis of this compound.

RESULTS AND DISCUSSION

Thirteen compounds (3, 4a-4d, 5a-5d, and 6a-6d) were screened for their antifungal activity at a concentration of 100mg/Lt and the results are reported in table I and table II. Some of the compounds were found to be inactive while others displayed mild to moderate as well as good activity .

Discussion of Table I & Table II

Compound 3 was devoid of any antifungal activity towards all the Candida species used.

Table-I
Pharmacological data of compounds 3, 4a-4d, 5a-5d, 6a-6d

Compounds	Antifungal activity# [diameter of inhibition zone (mm)]				
	Candida albicans	Candida albicans ATCC	Candida knusei GO3	Candida grabrata HO5	Candida parapsiolsis 22019
@ Control	0	0	0	0	0
Fluconazole*	29	25	19	15	20
Griseofulvin*	25	26	18	16	22
3.	-	-	-	-	-
4a.	-	-	-	-	-
4b	-	12	-	14	-
4c.	-	10	-	12	-
4d.	5	-	-	-	-
5a.	12	15	-	-	-
5b.	15	15	12	-	-
5c.	10	12	-	10	-
5d.	9	-	-	-	-
6a.	15	17	10	-	-
6b.	31	20	27	-	21
6c.	20	16	-	-	16
6d.	14	15	-	-	16

Concentration was 100 µg/Lt. @ 10% DMSO is methanol.
– : No inhibition zone. * Standard drugs used for comparison.

Table-II
Pharamcological data of compounds 3, 4a-4d, 5a-5d, 6a-6d

Compounds	Antifungal activity# [Inhibition in percentage]		
	Aspergillus Fumigatus	Aspergillus Niger	Aspergillus Flavus
@ Control	0	0	0
Fluconazole*	-	90	84
Griseofuloin*	80	88	82
3.	-	-	-
4a.	-	-	-
4b	-	36	42
4c.	-	20	-
4d.	-	-	-
5a.	-	-	-
5b.	64	68	72
5c.	-	36	50
5d.	-	34	-
6a.	-	62	-
6b.	74	94	80
6c.	-	86	-
6d.	-	70	-

Concentration was 100 µg/Lt. @ 10% DMSO is methanol.
– : No inhibition zone. * Standard drugs used for comparison.

The characteristic feature of compound 4a-4d is the presence of arylidene moiety. It was found that substitution at 2-position of the thiadiazole ring induces a little bit of antifungal activity in the analogs. Though 4a was found to be fungal resistant but 4b, 4c, and 4d displayed antifungal activity against one or the other Candida species used. 4b bearing hydroxy group at ortho position of phenyl ring displayed an i.z of 12mm and 14mm against C.albicans ATCC and C.parapsilosis. 4c, with N,N-dimethyl group at para position of phenyl ring was found to be active against C.albicans ATCC and C.glabrata with an i.z of 10 mm and 12mm respectively. 4d having p-hydroxy and m-methoxy substitution in phenyl ring gave 5mm inhibition against C.albicans.

Furthermore, introduction of azetidinone ring in compounds 5a-5d enhances the antifungal activity to some extent as compared to their parent compound. 5a gave 12mm i.z against C.albicans and 15mm i.z against C.albicans ATCC. 5b was active against C.albicans, C.albicans ATCC and C.krusei, with an i.z of 15mm, 15mm and 12mm respectively. 5c exhibited inhibition of 10mm for C.albicans, 12mm for C.albicans ATCC, 10mm for C.glabrata. 5d diplayed 9mm i.z for C.albicans. Among all the derivatives (5a-5d), 5b with hydroxy group at ortho position of phenyl ring seems to be more efficacious than rest of the compounds.

Cyclisation of arylidine derivatives (4a-4d) into their corresponding thiazolidinones (6a-6d) increases the antifungal activity to a considerable level. It is interesting to note from the results that compound 6b exhibited more potent antifungal activity against C. albicans and C. krusei and almost equipotant against C. parapsilosis in comparison to standard drug used i.e fluconazole and griseofulvin.

6a gave inhibition against C.albicans of 15mm, C. albicans ATCC of 17mm, and C.krusei of 10mm. 6b inhibited C.albicans, C.albicans ATCC, C.krusei, and C.parapsilosis with an i.z of 31mm, 20mm, 27mm, and 21mm respectively. 6c displayed an i.z of 20mm, 16mm, and 16 mm for C.albicans, C.albicans ATCC, and C.parapsilosis respectively. 6d showed 14mm i.z for C.albicans, 15mm i.z for C.albicans ATCC, and 16mm i.z for C.parapsilosis.

Among compounds 4a-4d i.e arylidine derivatives 4a and 4d were devoid of any antifungal activity, 4b showed 36% inhibition against A.niger and 42% inhibition against A.flavus. 4c was active only against A.niger with an inhibition of 20%.

Compounds 5a-5d formed by cyclisation of arylidine derivatives (4a-4d) into their corresponding azetidinone moiety (5a-5d) enhanced the antifungal activity. 5a was fungal resistant, 5b displayed 64%, 68%, and 72% inhibition against A.fumigatus, A,niger, and A,flavus respectively. 5c was found to be active against A.niger and Afflatus with 36% and 50% inhibition respectively. 5d was active only against A.niger with 34% inhibition.

Compounds 6a-6d bearing thiazolidinone moiety displayed moderate to good antifungal activity. 6a was active against A.niger with 62% inhibition. 6b revealed 74%, 94%, and 80% inhibition against A.fumigatus, A.niger, and A.flavus respectiely. 6c displayed 86% against A,niger and was inactive against the rest two species. 6d showed activity only against A.niger with 70% inhibition.

It is interesting to note that though 5b displayed broad spectrum activity but none was comparable to the standard drugs used. 6b was most potant compound having inhibition better than fluconazole against A.fumigatus and A.niger and better than griseofulvin against A.niger . It was almost equipotent to the standard drugs against A.flavus. 6c was almost equipotent to gresiofulvin against A.niger.

CONCLUSION

From the above results and discussion following conclusion can be drawn.

- Substituted arylidene congeners (4a-4d) exhibited very mild antifungal activity.
- The presence of azetidinone ring in compounds (5a-5d) increases the activity to some extent and compounds exhibits mild to moderate antifungal activity.
- The presence of thiazolidinone ring in compounds (6a-6d) enhances the antifungal activity to a considerable level.
- Appearance of methoxy group at ortho position of phenyl ring plays a significant role in modulation of antifungal activity.

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