Synthesis, Characterization, and Antifungal Potential of Some New Derivatives of benzylidene and azetidinones

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Abstract

Schiff bases and azetidinones form an important structural class possessing wide spectrum of biological activities that include antibacterial and antifungal activity. A large number of fungicides are formulated as wettable powders; this is the form most commonly used for spray mixes.Nodern wettable powerders are easily wetted and disperse well in water . They simply inhibit fungus growth temporarily.If the fungus is freed from such substance, it would revive. Such a chemical is called a ‘’fungistat” and the phenomenon of temporarily inhibiting the growth is ‘’fungistasis” .Some other chemicals, like certain phenanthrene derivatives and Bordeaux mixture, may inhibit spore production without affecting the growth of vegetative fungistate hyphae.These are called ‘’antisporulaaaaants’’. 2-amino-5-chloro-4-phenyl thiazole condensed with appropriate ethanol and piperidine aromatic was refluxed on water bath for 1 hr.Various. obtaining gave benzylidins and then compound treated with triethylamine in dioxane with chloroacetyl chloride was added dropwise at 10^0C .The reaction mixture was reflux on water bath for 10 hours .and cooled separated was recrystallised from chloroform. The synthesized compounds showed moderate to good antifungal activity with respect to standard drugs

Keywords:, . 2-amino-5-chloro-4-phenyl thiazole EtOH , chloroacetyl chloride , antifungal activity

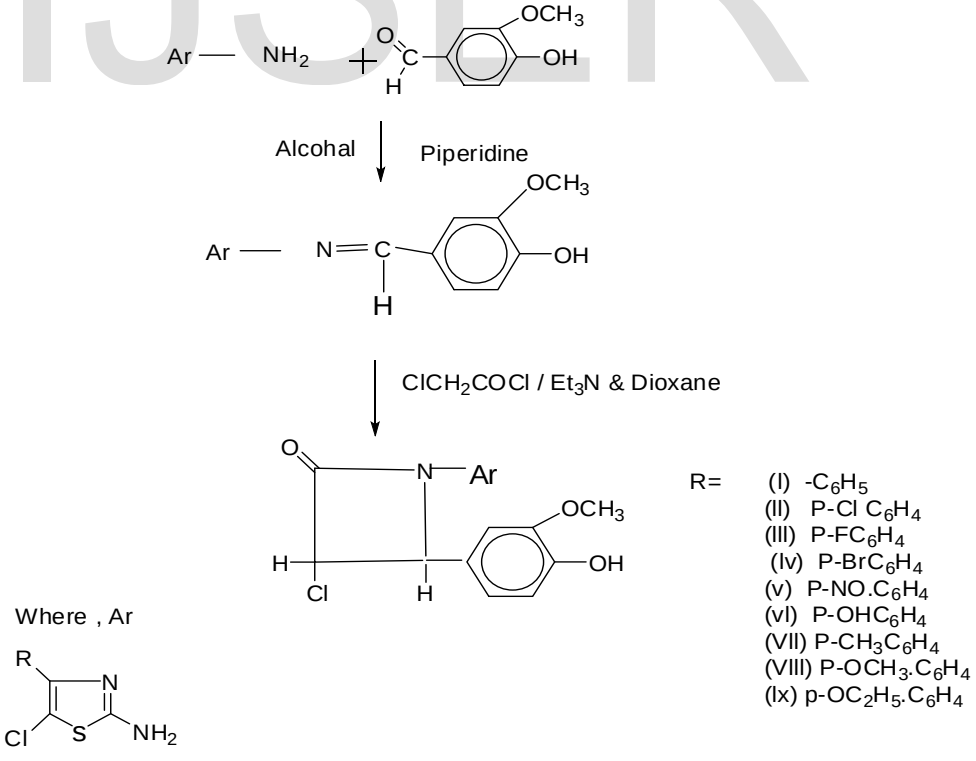
INTRODUCTION

Schief bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base. Stereochemical investigation carried out with the aid of molecular model showed that Schiff base formed between methylglyoxal and the amino group of the lysine side chains of proteins can bent back in such a way towards the N atom of peptide groups that a charge transfer can occur between these groups and oxygen atoms of the Schiff bases . Heterocyclic chemistry is currently experiencing arenaissance because of antiamoebic,61Azetidinones, commonly known as beta-lactams, are wellknown heterocyclic compounds among the organic and medicinal chemists .The activity of the famous antibiotics such as penicillin, cephalosporin, monobactams and carbapenems are attributed to the presence of azetidinone ring in them. Azetidin can be prepared from Schiff’s bases, which arethe condensation products of aldehydes and amino compounds. They are considered significant owing to their wide range of biological application. Recently, some other types of biological activity besides the antibacterial activity have been reported in compounds containing azetidinones ring. Such biological activities include antimicrobial, The structures of the various synthesizedcompounds were assigned on the basis of IR, 1H-NMR spectralNitrogen containing heterocyclic with sulfur atom is an important class of compounds in medicinal chemistry. Thiazoles being an integral part of many potent biologically active

molecules such as sulfathiazole (Antimicrobial drug), Ritonavir (Antiretroviral drug), Abafungin (Antifungal drug) with trade name Abase cream and Bleomycin and Tiazofurin (Antineoplastic drugs) have been explored previously

MATERIAL AND METHODS

Thiazoles are important class of natural and synthetic compounds. Thiazole derivatives display a wide range of biological activities such as cardiotonic,fungicidal,sedative, anesthetic ,bactericidal and anti inflammatory.The synthesis of thiazole derivatives is important of their wide range of pharmaceutical and biological properties .A large number of fungicides are formulated as wettable powders; this is the form most commonly used for spray mixes.Nodern wettable powerders are easily wetted and disperse well in water.A wetting agent is usually present in most wettable powder formulations, hand , fungicide which is capable of eradicating a fungus after it has caused infection and thereby ‘’curing” the plant, is called atherapeutant 8-quinolinol, antibiotics like Aureofungin,etc.Eradicants are those which remove pathogenic fungi from an infection court some chemicals do not kill fungi. The IR spectra were recorded on IR affinity-1, DRS-8000A, Shimadzu, Ptc. Ltd., Japan spectrophotometer. The 1H-NMR was recorded in DMSO on Bruker Advance II 400 MHz spectrometer using TMS as an internal standard. Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC-using Silica gel-G (Merck). Column chromatography was performed on silica gel. All the compounds were tested for their antibacterial and antifungal activities by broth dilution method. Nitrogen containing heterocyclic compounds



2-Amino-5-Chloro-4-(P-subst / Un-subst)-phenyl thiazole

Synthesis of [l] N-[5-Chloro-4-phenyl-2-Thiazolyl]-2-imino-[3'-methoxy-4-hydroxy]benzylidine

A mixture of 2-Amino-5-Chloro-4-phenyl Thiazole (0.01 mol) and vanillin (0.01) moles in ethanol 30 ml and piperidine 3-4 drops was refluxed on water bath for 2 hours . the reaction mixture was cooled and the solid separated was filtered and recrystallised from ethanol. Yield: (55%), m.p. 150^0C , IR(KBr) = 1210-1220 cm-1 (due to C-O-C) , 1665-1670 cm-^{1} ,(C=N) , 1590 - 1595 cm-1 (C=C) , 3000-3110 cm-^{1} (due to -OH) , 1640-1625 cm-1 and 1250 cm-1 (due to C=N and C-N) , 740-745 cm-^{1} (due to C-Cl). PMR = δ 4.0-4.2(3H,s.OCH_3) , δ 7.1-7.6(8H, m, ArH) , δ 8.2-8.5(1H,s =CH) , δ 9.5-9.7(1H, s,-OH) Similarly N-[5-Chloro-4-(p-subst/un-subst)-phenyl-2-Thiazolyl]-2-imino-[3'methoxy-4 hydroxy]benzylidine were prepared by using similar reaction procedure and their analytical data are incorporated in the table(l) respectively .

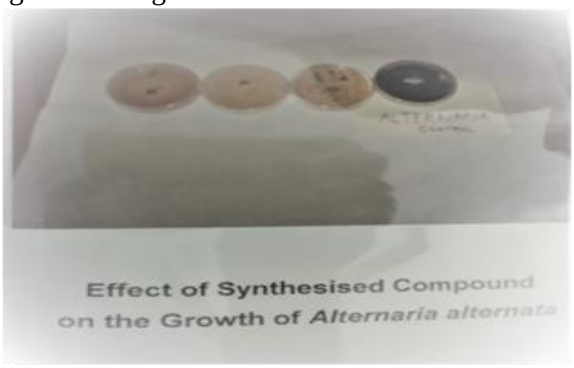
Synthesis of [ll] N-[5-Chloro-4-phenyl-2-Thiazolyl]-3'chloro-4"-[4'-hydroxyl-3'methoxy]-2'-azetidinones.

The compound first is treated with equimolar quantities of triethy amine. Dissolved in dioxane ,chloroacetyl chloride dropwise at 10^0C .The reaction mixture was refluxed on water bath fo 7 hours. The solvent was removed by distillation and cooled separated solid was recrystallised FromchloroformYield 62, M.P 210 ^{0}c IR(KBr) = 3110 cm-1 (due to -OH) , (due to cyclic > c=o), PMR= δ 3.82-3.95(3H,s OCH_3), δ4.52 cm-1(1H,D,-CHCl),δ7.3-8.25(8H,m,-Ar-H), δ4.1 – 4.6cm-^{1}(1H,d,-CH)Similarly,various, N-[5-Chloro-4(p-subst/un-subst)-phenyl-2-Thiazolyl]-3'chloro-4"-[4'-hydroxyl-3'methoxy]-2'azetidinones. Were prepared by using similar Reaction procedure and their analytical data are incorporated in the table-ll respectively.

RESULTS AND DISCUSSIONS

The synthesized compounds were carried out by broth micro dilution method as described by Rattan 2000. It is one of the non automated in vitro bacterial susceptibility tests. This classic method yields a quantitative result for the amount of antimicrobial agents that is needed to inhibit growth of specific microorganisms.The in vitro antimicrobial activity of test compounds were assessed against 24 hr cultures of several selected bacteria and fungi. The bacteria used were E. coli, and S. pyogenus; the fungi used were Aapergillus. Niger, . The antimicrobial activity was performed by broth dilution method in DMSO. Gentamycin, chloramphenicol, were used as standard for the evaluation of antibacterial and antifungal activities respectively.The activity was reported by minimalinhibition concentration. The results are summarized in table-2 , Biological screening result of of N-[4-phenyl(p-subbst/unsubst] thiazolyl)-3-Chloro-4"-(4'-hydroxyphenyl)-2-azetidinones based derivatives shows tha compound-1 have shown better activity against E. coli and S.pyogenus, while-5 have Shawn better activity against E.coli, while rest of all compound possessed good activity in the range of 100-225 µg/ml. Compounds with substitution p-Chloro (compound-1 &-6 shown good antibacterial activity against S. pyogenus , while rest of all derivatives possessed good activity against S. pyogenus in the range of 125-250 µg/ml. While rest of all derivatives are poor against A. Niger.

TABLE- 1



S. N.	Nature of Ar	Molecular Formula	Yield %	M.P. ^{O}C	ELEMENTAL ANALYSIS			
					% of N		% of S	
					Cald	Fond	Cald	Found
la	2-Amino-5-chloro-4-phenyl Thiazole	$C_{17}H_{13}N_2O_2SCl$	42	138	9.03	09.00.	10.32	10.25
lb	2-Amino-5-chloro-4-(p-chloro)-phenyl thiazole	$C_{17}H_{13}N_2O_2SCl_2$	50	140	19.92	19.86	22.77	22.69
lc	2-Amino-5-chloro-4-(p-fluoro)-phenyl Oxazole	$C_{17}H_{13}N_2O_2SFCl$	52	145	08.53	08.50	09.75	09.70
ld	2-Amino-5-chloro-4-(p-bromo)- phenyl thiazole	$C_{17}H_{13}N_2O_4SBrCl$	48	106	07.21	07.11	08.24	08.20
le	2-Amino-5-chloro-4-(p-nitro)- phenyl thiazole	$C_{18}H_{12}N_3O_4SI$	47	148	11.83	11.76	09.01	08.93
lf	2-Amino-5-chloro-4-(p-hydroxy) phenyl thiazole	$C_{17}H_{13}N_3O_4SCl$	48	165	08.3	08.49	09.75	09.73
lg	2-Amino-5-chloro-4-(p-methyl)- phenyl thiazole	$C_{18}H_{15}N_2O_2SCl$	52	226	08.4	08.60	09.87	09.80
lh	2-Amino-5-chloro-4-(p-methoxy)- phenyl thiazole	$C_{18}H_{16}N_2O_3SCl$	53	246	08.23	08.20	09.41	09.35
li	2-Amino-5-chloro-4-(p-ethoxy) phenyl thiazole	$C_{19}H_{18}N_2O_3SCl$	50	250	07.90	07.80	09.03	09.00

TABLE- ll

N-[5-Chloro-4(p-subst/un-subst)-phenyl-2-Thiazolyl]-3'chloro-4"-[4'-hydroxyl-3'methoxy]-2'azetidinones.

S. N.	Nature of Ar	Molecular Formula	Yield %	M.P. ^{O}C	ELEMENTAL ANALYSIS			
					% of N		% of S	
					Cald	Fond	Cald	Found
lla	2-Amino-5-chloro-4-phenyl Thiazole	$C_{19}H_{14}N_2O_4Cl_2$	52	179	07.09	07.05	16.24	16.22
llb	2-Amino-5-chloro-4-(p-chloro)-phenyl thiazole	$C_{19}H_{13}N_2O_3Cl_3$	53	190	06.50	06.45	14.93	14.90
llc	2-Amino-5-chloro-4-(p-fluoro)-phenyl Oxazole	$C_{19}H_{13}N_2O_3SCl_2F$	50	185	06.54	06.50	15.05	15.00
lld	2-Amino-5-chloro-4-(p-bromo)- phenyl thiazole	$C_{19}H_{13}N_2O_3BrCl_2$	42	186	05.93	05.88	13.55	13.52
lle	2-Amino-5-chloro-4-(p-nitro)- phenyl thiazole	$C_{19}H_{13}N_3O_6SCl_2$	50	225	09.56	09.49	14.97	14.55
llf	2-Amino-5-chloro-4-(p-hydroxy) phenyl thiazole	$C_{19}H_{14}N_2O_4SCl_2$	42	48	06.82	06.78	15.60	15.55
llg	2-Amino-5-chloro-4-(p-methyl)- phenyl thiazole	$C_{20}H_{16}N_2O_3SCl_2$	51	44	06.86	06.81	15.68	15.60
llh	2-Amino-5-chloro-4-(p-methoxy)-phenyl thiazole	$C_{19}H_{16}N_2O_3SCl_2$	50	41	06.60	06.55	15.09	14.55
lli	2-Amino-5-chloro-4-(p-ethoxy) phenyl thiazole	$C_{21}H_{18}N_2O_4SCl_2$	54	45	06.39	06.20	14.61	14.02

RESULT AND DISCUSSION :

It is evident from fungal screening data that all the newly synthesized compound tested were found satisfactorially superior over control but inferior to that of standard antifungal (Bavistin) compoundmostly synthesized compound showed marked of the fungal growth in vitro test . It can also be concluded from the result that mostly synthesized compound are good antifungal and showed significant level of antifungal activity and .compound No(lg) showed moderate activity.

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