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Polymers Derived from 4-Substituted Salicylic Acids as Antifungal Agents

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ABSTRACT

4-Amino-, chloro-, and bromo-substituted salicylic acid-formaldehyde polymers and their metal chelates were screened for their antifungal activity. Various copolymers prepared from 4-chloro-(bromo)salicylic acid, formaldehyde, and other comonomers were also screened for their antifungal activity. All these polymers, copolymers, and polychelates were found active against several fungi Their fungicidal activities are compared with those of the corresponding monomers and monomeric chelates.

INTRODUCTION

Salicylic acid and its derivatives are known for their biological activity. Salicylic acid, its derivatives, and also its metal chelates have been reported to be antifungal agents [1-4]. p-Aminosalicylic acid (PAS) is a well-known antituberculosis drug, and 4-chloro (CS) and

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4-bromosalicylic acids (BS) are known for their antituberculosis and fungicidal activities [5, 6].

Polymers derived from salicylic acid and its derivatives are also known for their biological activity [7-10]. Salicylic acid-formaldehyde (SF) polymers having the salicylic acid nucleus incorporated into their polymer backbone could possess enhanced bioactivity. Such types of polymers could act as antibradykinins [11] and could also inhibit the attachment of HeLa cells growing in human serum [12]. The fungicidal activity of amide derivative of salicylic acid-p-tert-butyl phenol-formaldehyde copolymer has also been investigated [13]. Ciampa and his co-workers [8] carried out a good deal of work on SF-type polymers. They prepared several esters of salicylic acid and N-arylsalicylamide derivatives, polycondensed them with formaldehyde, and tested them for biological activity.

One of the authors (H.S.P.) has reported [14-17] the synthesis, characterization, and/or chelating properties of p-aminosalicylic acid-formaldehyde (PAS-F), p-chlorosalicylic acid-formaldehyde (CS-F), p-bromosalicylic acid-formaldehyde (BS-F) polymers and copolymers derived from CS or BS, formaldehyde and comonomer like salicylic acid (SA), p-hydroxybenzoic acid (PHBA), PAS, p-aminobenzoic acid (PABA), p-cresol (PC), p-chlorophenol (PCP), and p-bromophenol (PBP). In view of the reported properties of SF polymers, these polymers could be expected to possess bioactivity. Hence the present work, comprising evaluation of antifungal activity of the polymers, polymeric chelates, and copolymers listed in Tables 1-4, was undertaken.

EXPERIMENTAL

Materials

PAS was regenerated from sodium-p-aminosalicylate (Na-PAS) obtained from Cadila Laboratories, Ahmedabad, India. Other chemicals used were of Analar or chemically pure grade.

To test the fungicidal activity of polymers, polymeric chelates, and copolymers, various plant pathogenic organisms (Penicillium expansum, Botrydepladia thiobromine, Nigrospora sp., Trichothesium sp., and Rhizopus nigricans) were employed.

Preparation of Monomers and Monomeric Chelates

4-Chlorosalicylic acid (CS) and 4-bromosalicylic acid (BS) were prepared by reported methods [16, 18]. Their sodium salts (Na-CS and Na-BS) were prepared by evaporating the neutral solution prepared by reaction of CS or BS with a cold, dilute, aqueous solution of sodium hydrogen carbonate.

TABLE 1. Antifungal Activity of p-Aminosalicylic Acid (PAS) and Its Metal Chelates (PAS-metal), and PAS-Formaldehyde (PAS-F) Polymer and Its Metal Chelates (PAS-F-metal) [14]

Sample	Zone of inhibitions at 1000 ppm (%)				
	Penicillium expansum	Botrydepladia thiobromine	Nigrospora sp.	Trichothesium sp.	Rhizopus nigricans
PAS	100	100	79	100	100
Na-PAS	100	100	100	100	75
PAS-Cu(II)	100	72	81	100	100
PAS-Fe(III)	75	62	100	100	78
PAS-Ni(II)	55	30	100	42	100
PAS-Co(II)	100	70	100	100	100
PAS-F	100	82	72	80	100
Na-PAS-F	100	100	100	77	63
PAS-F-Cu(II)	82	80	70	85	90
PAS-F-Fe(III)	100	60	100	100	85
PAS-F-Ni(II)	50	17	100	35	100
PAS-F-Co(II)	100	62	100	100	100

TABLE 2. Antifungal Activity of 4-Chlorosalicylic Acid (CS) and Its Metal Chelates (CS-metal) and CS-Formaldehyde Polymer (CS-F) and Its Metal Chelates (CS-F-metal) [15]

Sample	Zone of inhibitions at 1000 ppm (%)				
	Penicillium expansum	Botrydepladia thiobromine	Nigrospora sp.	Trichothesium sp.	Rhizopus nigricans
CS	100	100	100	100	100
Na-CS	100	100	100	89	85
CS-Cu(II)	100	73	100	100	100
CS-Fe(III)	100	100	100	65	100
CS-Ni(II)	76	100	100	100	100
CS-Co(II)	100	80	85	90	82
CS-F	100	100	100	100	86
Na-CS-F	70	100	100	68	85
CS-F-Cu(II)	83	63	84	83	78
CS-F-Fe(III)	80	83	100	55	100
CS-F-Ni(II)	64	73	70	70	65
CS-F-Co(II)	82	75	70	78	67

TABLE 3. Antifungal Activity of 4-Bromosalicylic Acid (BS) and Its Metal Chelates (BS-metal) and BS-Formaldehyde Polymer (BS-F) and Its Metal Chelates (BS-F-metal) [16]

Sample	Zone of inhibitions at 1000 ppm (%)				
	Penicillium expansum	Botrydepladia thiobromine	Nigrospora sp.	Trichothesium sp.	Rhizopus nigricans
BS	100	100	100	100	100
Na-BS	100	100	100	83	80
BS-Cu(II)	100	70	100	100	100
BS-Fe(III)	100	100	100	60	100
BS-Ni(II)	80	100	100	100	100
BS-Co(II)	100	75	80	85	78
BS-F	100	100	100	85	80
Na-BS-F	100	80	100	65	60
BS-F-Cu(II)	85	55	100	100	100
BS-F-Fe(III)	100	100	90	50	100
BS-F-Ni(II)	40	100	100	90	100
BS-F-Co(II)	85	54	65	82	79

TABLE 4. Antifungal Activity of Copolymers Prepared from 4-Chloro(bromo)salicylic Acid (CS or BS), Formaldehyde, and Other Comonomers [17]

	Zone of inhibitions at 1000 ppm (%)				
Sample[a]	Penicillium expansum	Botrydepladia thiobromine	Nigrospora sp.	Trichothesium sp.	Rhizopus nigricans
CS.SA.F	100	85	75	80	100
BS.SA.F	100	90	80	87	100
CS.PHBA.F	100	76	75	88	100
BS.PHBA.F	100	65	80	82	100
CS.PAS.F	100	81	100	100	86
BS.PAS.F	100	75	100	90	80
CS.PABA.F	100	65	75	100	100
BS.PABA.F	100	60	70	82	100
CS.PC.F	77	45	60	83	30
BS.PC.F	70	40	55	74	35
CS.PCP.F	100	85	100	100	100
BS.PBP.F	100	77	85	100	100

[a]SA = salicylic acid, PHBA = p-hydroxybenzoic acid, PAS = p-aminosalicylic acid, PABA = p-aminobenzoic acid, PC = p-cresol, PCP = p-chlorophenol, PBP = p-bromophenol.

Metal chelates Cu(II), Fe(III), Ni(II), and Co(II) of PAS, CS, and BS were prepared by mixing aqueous solutions of Na-PAS, Na-CS, or Na-BS and aqueous metal salts in stoichiometric ratios. The metal content of each monomeric chelate was estimated volumetrically [19]. The results of the metal composition of each monomeric chelate suggest that the metal-ligand (M:L) ratio is 1:2 for Cu(II), Ni(II), and Co(II) metal ions and 1:3 for Fe(III) metal ions.

Monomers, their sodium salts, and metal chelates employed for the study of bioactivity are listed in Tables 1 to 3.

Preparation of Polymers and Polymeric Chelate

PAS-F, CS-F, and BS-F polymers and their sodium salts and metal [Cu(II), Fe(III), Co(II), Ni(II)] chelates listed in Tables 1-3 were prepared by methods described in earlier communications [14-16].

Preparation of Copolymers

Copolymers like CS.SA.F, BS.SA.F, CS.PHBA.F, BS.PHBA.F, CS.PAS.F, BS.PAS.F, CS.PABA.F, BS.PABA.F, CS.PC.F, BS.PC.F, CS.PCP.F, and BS.PBP.F were prepared by methods described in an earlier communication [17].

Antifungal Activity

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were Penicillium expansum, Botrydepladia thiobromine, Nigrospora sp., Trichothesium sp. and Rhizopus nigricuns. The antifungal activity of all monomers and polymer samples was measured on each of these plant pathogenic strains on a potato dextrose agar medium (PDA). Such a PDA medium contained [20] potato 200 g, dextrose 20 g, agar 20 g, and water 1 L. Five day-old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120°C for 15 min at 15 atm pressure. These media were poured into sterile Petri plates, and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after 5 d using the formula given below.

$$\text{Percentage of inhibition} = \frac{100(X - Y)}{X}$$

where X = area of colony in control plate
Y = area of colony in test plate

The fungicidal activity displayed by various monomers and polymer samples is shown in Tables 1-4.

RESULTS AND DISCUSSION

The toxic effect of salicylic acid and its derivatives and its metal chelates against bacteria or fungi has been reported [1-4]. However, there is no information in the literature about the antimicrobial activity of such substituted salicylic acids as p-aminosalicylic acid (PAS), 4-chlorosalicylic acid (CS), and 4-bromosalicylic acid (BS) except for a few instances [6, 21-23]. Hence, for comparison of the bioactivity of polymers, the antifungal activity of these monomeric acids and their metal chelates is also presented here.

Examination of the results reported in Tables 1-3 reveals that the polymers and polychelates are equally or less toxic against various fungi than the corresponding monomers and their chelates. However, monomers and their chelates are also toxic against fungi at 500 ppm concentration. With a view to comparing the activity of polymers and their chelates with these monomers and their chelates, 1000 ppm concentrations of monomers and their chelates were taken.

The results presented in Table 1 show that PAS-F polymer and its Na-salt are slightly less active than PAS. The fungicidal activity of the PAS-metal chelates is slightly less than that of PAS. However, PAS-F-metal chelates (polychelates) and their corresponding monomeric metal chelates do not differ much in their antifungal properties. This may be due to the insolubility of monomeric and polymeric chelates. The results also show that PAS-Co(II) and PAS-F-Co(II) chelates are more active than the other chelates.

The results presented in Tables 2 and 3 show that CS, BS, and their Na-salts are highly toxic against fungi. The polymers CS-F and BS-F and their Na-salts are also toxic against fungi. These monomers and the polymers derived therefrom do not differ much in their fungicidal activity. However Na-salts of the polymers are found to possess a slightly lower fungicidal effect. The fungicidal activity of chelates of CS and BS is nearly the same as that of CS and BS acids. Their corresponding polymeric chelates possess a lower fungicidal activity. It was also found that polymeric chelates containing Fe(III), Cu(II), and Ni(II) ions have a higher activity than polymeric chelates containing the Co(II) ion.

Examination of the results of antifungal activity of copolymers reported in Table 4 also reveals that all copolymers are toxic against fungi. All the copolymers except CS.PC.F and BS.PC.F comprise bioactive comonomers have fungicidal activity in the range of 65-100% depending upon the nature of the fungi. The smaller activity of

CS.PC.F and BS.PC.F copolymers may be due to the lower composition of CS or BS units [17] in the copolymers.

Comparison of the results presented in Tables 1-4 reveals that CS-F, BS-F, CS.PAS.F, BS.PAS.F, CS.PCP.F, and BS.PBP.F have a higher fungicidal activity than the other polymer or copolymers. This higher activity may be due to the presence of a halogen (Cl, Br) in the polymer or copolymer. Polymeric chelates have slightly less fungicidal activity than the corresponding parent polymers. The toxic effect of polymers and their metal chelates and copolymers against Penicillium expansum, Nigrosora sp., and Rhizopus nigrican strains is the 80-100% range.

Most of the polymers and polymeric chelates inhibit the growth of the above organism which cause disease in many plants. Hence, such type of polymers may find use as agricultural and garden fungicides.

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