Synthesis and fungicidal activity of 4,4′-bis[*N*-(2″-aryl-5″-methyl/unsubstituted-4″-thiazolidinon-3″-yl)acetamidoxy] bibenzyl

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Abstract

Diazotization of 4,4'-diaminobibenzyl (I) with sodium nitrite and HCl at 0-5°C followed by hydrolysis gave 4,4'-dihydroxybibenzyl (II), which on reaction with chloroacetic acid in presence of sodium carbonate yielded 4,4'-ethylenebisphenoxyacetic acid (III). Nucleophilic substitution of compound (III) with hydrazine hydrate gave 4,4'-bis(methoxycarbohydrazide)bibenzyl (IV), which on condensation with different carbonyl compounds gave 4,4'-bis(arylidinylaminoacetamidoxy)bibenzyls (Va-f). Compounds (Va-f) on cycloaddition with mercaptoacetic acid/2-mercaptopropionic acid yielded the corresponding 4-oxothiazolidin-3-yl bibenzyls (VIa-l).

Compounds (Va-f) and (VIa-l) have been screened for their antifungal activity against two fungal species viz: Aspergillus niger and Fusarium oxysporum. A possible relationship between screened results and structural features of the tested compound has been deduced and compared with commercial fungicide Dithane M-45. All the compounds were found to be antifungal active. Some of the compounds inhibited the growth of fungus upto 82% to 100% at 1000ppm comparable with that of the commercial fungicide Dithane M-45.

Keywords: Bibenzyl, thiazolidinone, fungicidal activity, *Aspergillus niger* and *Fusarium oxysporum.*

Introduction

Bibenzyl derivatives are naturally occurring potential fungicides. It has been found that natural as well as synthetic bibenzyls both show antifungal activity. By virtue of wide variations possible in the properties of various heterocycles, they are adaptable candidates required for the specialized reactivities required in the chemistry of living organisms. With the hope of further exploring new antifungal bibenzyls having heterocyclic moieties, it was considered to synthesize new potentially bio-active, safe, environment friendly fungicides with aim to increase permeability into the fungal cell. Presently fungicides play an important role to boost up the production of agricultural crops, industrial production prolonging the utility of manufactured products and controlling the various human and fungal diseases. In view of the aforesaid acts of fungi, one may very well understand the importance of fungitoxic chemicals in agriculture as well as in industry.

Literature survey on bryophytes has shown that bryophytes as well as extract of the chemical constituent of bryophytes are not damaged by fungi. The reason why bryophytes are not affected by fungus is the presence of structural variants of bibenzyls *viz*. lunularic acid and lunularin and bis bibenzyl *viz* plagiochin, marchatia etc. It has been found that natural as well as synthetic bibenzyls both show antifungal activity.[1] Bibenzyl are the important natural products and have attracted considerable interests due to their biological activities[2].

The occurrence of the bibenzyls in nature in limited amount in rather inaccessible plant species has increased the need for good synthetic methods. They have low toxicity to mammal and higher plants because they are biodegraded into primary metabolities viz phenylene and acetic acid. Thiazolidinones[3-6] are known to possess various biological activities. Thiazolidinones exhibit anticonvulsant activity, anti–inflammatory activity, anti-tubercular activity, anthelmintic activity, antiviral activity, antifungal activity, antibacterial activity, anticancer activity and anti-HIV activity, anticonvulsant and anaesthetic properties[7-16].

Prompted by these observations we undertook the synthesis of heterocyclic compounds in which thiadiazoles moieties are present. When these moieties are attached with bibenzyl, which itself is antifungal, its activity increases many folds. In continuation of our research work,[17-24] we synthesized new bibenzyl incorporating thiazolidinone moieties.

Material and Methods

All chemicals used were of reagent grade and were used as received without further purification. Solvents were of reagent grade and dried using standard procedures. All m.p.s were taken in open capillary tubes and are uncorrected. The structural assignments of the synthesized products were based on elemental analysis carried out using a Coleman automatic carbon, hydrogen and nitrogen analyzer, 1H NMR spectra were recorded by using DMSO-d6 on a Bruucker DRX-300 (300 MHz FTNMR) spectrometer using TMS as internal reference and mass spectra were recorded on a JEOL D-300 mass spectrometer at 70 eV.

4,4′-Ethylenebisphenoxyacetic acid III: The solution of ethylene bisphenol II[16] (0.03mol) in dry acetone (25ml), anhydrous K_2CO_3 (10g) and chloroacetic acid (0.03 mol)

was added and refluxed on a water bath with stirring for 12-13 h under reduced pressure. The product was filtered, dried and crystallized from ethanol to obtain analytically pure III.

4,4′-Bis(methoxycarbohydrazide)bibenzyl IV: A mixture of III (0.05mol) and hydrazine hydrate (0.06mol) in absolute ethanol (25ml) was refluxed on a steam-bath. After refluxing for 4h, excess of ethanol was distilled, the solid mass thus obtained was filtered, dried and recrystallized from ethanol to obtain analytically pure IV.

4,4′-Bis(arylidinylaminoacetamidoxy)bibenzyl Va-f: A mixture of IV (0.01mol), verataldehyde(0.01mol) and a few drops of glacial acetic acid in ethanol(10 ml) was refluxed for 5 h and then cooled. The resulting solid was washed with cold ethanol and recrystallized from aqueous ethanol to get Va (61%). Other compounds Vb-f were synthesized by a similar procedure using various aldehydes (anisaldehyde, salicyaldehyde, p-hydroxybenzaldehyde, p-chlorobenzaldehyde and p-nitrobenzaldehyde in place of verataldehyde).

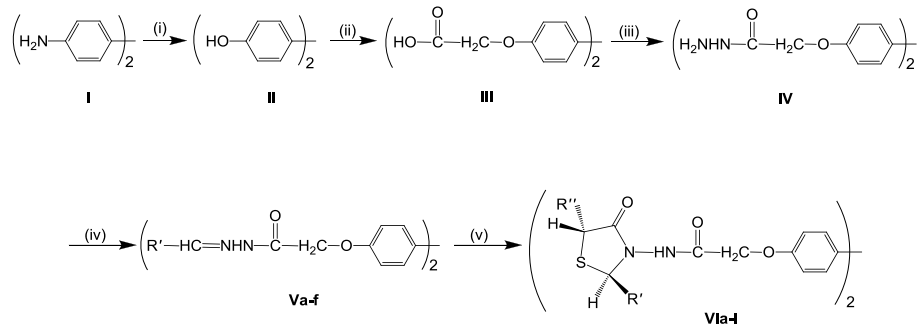
4,4′-bis[*N*-(2″-aryl-5″-methyl/unsubstituted-4″thiazo lidinon-3″-yl)acetamidoxy] bibenzyls VIa-l: A mixture of Va-f (0.01mol) and thioglycollic acid/mercaptopropionic acid (0.01mol) in dioxane (30ml) was refluxed for 6h. The excess dioxane was then distilled off under reduced pressure and the residue poured in ice cold water. The solid, thus obtained was washed with 10% sodium bicarbonate solution finally with cold water and recrystallised from aqueous ethanol to give VIa-l.

Antifungal Screening: The synthesized compounds Va-fand VIa-l have been screened for their fungicidal activity against two fungal species viz. *Aspergillus niger* and *Fusarium oxysporum* by using following agar plate technique[1]. The antifungal activity of each compounds was evaluated at three different concentrations viz. 1000 ppm, 100ppm and 10 ppm. After 96 hours at 28°C, four diameters of fungal colony intersecting one another at about 45° were measured by means of a millimeter scale. Inhibition of fungal growth was determined as the differences in growth between control plates and those treated with test compounds. The percentage inhibition of mycelia growth was calculated by the following equation:

%inhibition=100x(C-T)/C

where C= Average diameter of fungal colony (in mm) in control plates and T= Average diameter of fungal colony (in mm) in tested plates.

Scheme 1



Scheme condition:

(i)a. HCl, $NaNO_2$, 0.0 to -5°C, **b.** $H^{\oplus}/\Delta$

(ii). $Cl\text{-}CH_2COOH$, K_2CO_3/ dryacetone

(iii). $NH_2NH_2.H_2O$

(iv). R′–CH=O

(v). HS-CH.COOH
R″

Compd.	R’	R”	Compd.	R’	R”
Va	3,4-$(CH_3O)_2.C_6H_3$	-	VId	4-$OH.C_6H_4$	H
Vb	4-$CH_3O.C_6H_4$	-	VIe	4-$Cl.C_6H_4$	H
Vc	2-$OH.C_6H_4$	-	VIf	4-$NO_2.C_6H_4$	H
Vd	4-$OH.C_6H_4$	-	VIg	3,4-$(CH_3O)_2.C_6H_3$	CH_3
Ve	4-$Cl.C_6H_4$	-	VIh	4-$CH_3O.C_6H_4$	CH_3
Vf	4-$NO_2.C_6H_4$	-	VIi	2-$OH.C_6H_4$	CH_3
VIa	3,4-$(CH_3O)_2.C_6H_3$	H	VIj	4-$OH.C_6H_4$	CH_3
VIb	4-$CH_3O.C_6H_4$	H	VIk	4-$Cl.C_6H_4$	CH_3
VIc	2-$OH.C_6H_4$	H	VIl	4-$NO_2.C_6H_4$	CH_3

The antifungal activity displayed by various groups of compounds is reported in table 1. For the highly active compound, it was ascertained whether these were fungistatic or fungicidal. Thus, following the procedure of poison food method, the compounds were added separately to PDA medium in different Petri plates to maintain the final concentrations at their respective lethal doses. The test fungi were inoculated in the centre of these Petri plates and incubated at 28^0C for 96 hr. and percent inhibition was recorded following the procedure of Garbure and Houstan.[17]

Results and Discussion

Reaction of 4,4′ dihydroxybibenzyl in dry acetone with chloroacetic acid and potassium carbonate gave 4,4′-ethylenebisphenoxyacetic acid III which on refluxing with hydrazine hydrate yielded 4,4′– bis (methoxycarbohydrazide)bibenzyl IV. Compound IV on condensation with different aromatic aldehydes gave 4,4′-bis benzylidinylaminoacetamidoxy)bibenzyls Va-f. Reaction of Va-f with thioglycollic acid/ mercaptoproponoic acid gave 4,4′- bis[*N*-(2″-aryl-5″-methyl/unsubstituted-4″-thiazolidinon-3″-yl)acetamidoxy]bibenzyls VI a-l **(**Scheme 1).

Compounds Va-f and VIa-l were screened for their antifungal activity against *Fusarium oxysporum* and *Aspergillus niger* at 10, 100 and 1000 ppm concentration by agar plate technique[15]. A commercial fungicide dithane M-45 {a mixed Mn^{2+} and zinc salt of *N, N′*-ethylenebis (dithiocarbamic acid)} was also tested under similar condition for comparing the results. Among the tested compounds, VIe, VIf, VIk, VIl were found to be most active against both the test fungus (Table 1).

Conclusion

In general, nine derivatives of thiazolidinone incorporating bibenzyl were successfully synthesisized from the reaction. The antifungal activity revealed that the compound VIf as the most potent antifungal agent against *Aspergillus niger* and *Fusarium oxysporum* bacteria. Further research is needed to investigate other potential activities of derivatives of thiazolidinone.

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Table 1
Antifungal Screening Results of compounds Va-f and VI a-l

Average % inhibition after 96h against						
Compound	***Aspergillus niger***			***Fusarium oxysporum***		
	1000ppm	**100ppm**	**10ppm**	**1000ppm**	**100ppm**	**10 ppm**
Va	49	26	13	51	29	15
Vb	45	20	18	41	32	8
Vc	53	42	25	56	39	19
Vd	61	43	20	53	36	19
Ve	58	37	22	63	46	23
Vf	63	45	31	69	37	26
VIa	62	30	15	58	32	18
VIb	52	34	12	59	31	10
VIc	70	54	27	68	51	25
VId	60	49	17	64	43	28
VIe	82	65	43	86	69	42
VIf	100	82	52	100	78	51
VIg	69	45	25	65	38	21
VIh	72	56	40	73	46	24
VIi	75	58	42	76	59	46
VIj	56	41	22	53	39	19
VIk	83	67	45	81	65	47
VIl	91	79	51	93	81	50

Table 2
Physical and spectral data of compounds III,IV,Va-f and VI a-l

Com.	Mol. Formula	M.P.°C	MS m/z	^{1}H NMR (δ)	% Analysis Found		
					C	H	N
III	$C_{18}H_{18}O_6$	260	330	2.82 (4H, s, acyclic CH_2-, 7.1-7.9 (8H, m, ArH), 4.94 (s, 4H, OCH_2), 2.5 (s, 2H, COOH)	62.95 63.15	5.12 5.26	
IV	$C_{18}H_{22}O_4N_4$	100	358	2.81(s, 4H, acyclic CH_2-CH_2), 7.1-7.9 (m, 8H, ArH), 4.94 (s, 4H, OCH_2), 8.1 (s, 2H, NHCO), 4.65-5.25 (s, 4H, NH_2)	60.12 60.35	5.95 6.14	14.8 14.8
Va	$C_{36}H_{38}O_8N_4$	65	598	2.89 (4H,s,acyclic CH_2-CH_2), 3.93(6H,s,OCH_3), 3.95(6H,s,OCH_3)4.95 (4H, s, OCH_2), 7.12-7.85 (14H, m, ArH), 8.28(2H, s, CH=N), 8.31 (2H, s, NH-N)	65.98 66.05	5.61 5.81	8.51 8.56
Vb	$C_{34}H_{34}O_6N_4$	160	594	2.87 (4H, s, acyclic CH_2-CH_2), 3.93 (6H, s, OCH_3), 4.95(4H, s, OCH_2), 7.12-7.65 (16H, m, ArH), 8.25 (2H, s, CH=N), 8.31 (2H, s, NH-N)	67.12 67.32	5.2 5.6	9.13 9.24
Vc	$C_{32}H_{30}O_6N_4$	205	566	2.85 (4H, s, acyclic CH_2-CH_2), 4.95 (4H, s, OCH_2), 7.12-7.65 (16H, m,ArH), 8.29(2H, s, CH=N), 8.31 (2H, s, NH-N) 12.1 (2H, s, ArOH)	66.03 66.4	5.03 5.19	9.23 9.68
Vd	$C_{32}H_{30}O_6N_4$	165	566	2.85 (4H, s, acyclic CH_2-CH_2), 4.95 (4H, s, OCH_2), 7.21-7.53 (16H, m, ArH), 8.31(2H, s, CH=N), 8.31(2H, s, NH-N), 11.69 (2H, s, ArOH)	66.03 66.4	5.03 5.19	9.23 9.68
Ve	$C_{32}H_{28}O_4N_4Cl_2$	185	634	2.87 (4H, s, acyclicCH_2-CH_2), 4.96 (4H, s, OCH_2), 7.12-7.83 (16H, m, ArH), 8.31(2H, s, CH=N), 8.33 (2H, s, NH-N)	63.2 63.6	4.60 4.64	9.08 9.28
Vf	$C_{32}H_{28}O_8N_6$	180	592	2.82 (4H, s, acyclicCH_2-CH_2), 4.96 (4H, s, OCH_2), 7.08-7.25 (16H, m, ArH), 8.33 (2H, s, CH=N), 8.33 (2H, s, NH-N)	61.2 61.5	4.1 4.4	13.23 13.46
VIa	$C_{40}H_{42}N_4O_{10}S_2$	165	802	2.84 (4H, s, acyclicCH_2-CH_2), 3.93 (6H, s, OCH_3), 3.95 (6H, s, OCH_3), 4.30 (4H, s, cyclic, $COCH_2$-S), 4.95 (4H, s, OCH_2), 5.92 (2H, s, cyclic-CH-N), 7.12-7.85 (14H, m ,ArH), 8.34 (2H, s, NH-N),	59.65 59.85	5.12 5.23	6.89 6.90
VIb	$C_{38}H_{38}N_4O_8S_2$	160	742	2.84 (4H, s,acyclicCH_2-CH_2), 4.30 (4H,s,cyclic,CO-CH_2-S), 4.90(4H, s,OCH_2), 5.50 (2H,s,cyclicCH-N), 7.12-7.85 (16H, m ArH), 8.30(2H, s,NH-N),	61.1 6.14	5.08 5.12	7.34 7.54
VIc	$C_{36}H_{34}N_4O_8S_2$	200	714	2.85 (4H,s,acyclicCH_2CH_2), 4.30 (4H,s,cyclicCO-CH_2-S), 4.90(4H,s,OCH_2), 5.50 (2H,s,cyclicCH-N), 7.12-7.53 (16H,m,ArH), 8.34(2H,s,NH-N), 12.12 (2H,s,ArOH),	60.1 60.5	4.56 4.76	7.75 7.84
VId	$C_{36}H_{34}N_4O_8S_2$	182	714	2.85 (4H,s,acyclicCH_2CH_2), 4.30 (4H,s,cyclicCO-CH_2-S), 4.95(4H,s,OCH_2), 7.12-7.53(16H,m,ArH), 11.69 (2H,s,ArOH), 8.01(2H,s,NHCO), 8.34(2H, s,NH-N),	60.2 60.5	4.68 4.76	7.79 7.75
VIe	$C_{36}H_{32}N_4O_6S_2Cl_2$	180	750	2.87 (4H, s, acyclicCH_2CH_2), 4.30 (4H, s, cyclicCO-CH_2-S), 7.25-7.97 (16H, m, ArH), 4.97 (4H, s, OCH_2), 8.01 (2H, s, NHCO), 8.34 (2H, s, NH-N)	59.9 60.08	4.4 4.45	7.65 7.78
VIf	$C_{36}H_{32}O_{10}N_6S_2$	217	772	2.89 (4H, s, acyclicCH_2CH_2), 7.25-7.96 (16H, m, ArH), 4.95(4H, s, OCH_2), 8.01(2H, s, NHCO), 8.34 (2H, s, NH-N), 4.30 (4H, s, cyclicCO-CH_2-S)	55.82 55.95	4.7 4.14	10.1 10.8
VIg	$C_{42}H_{46}N_4O_{10}S_2$	210	830	1.22 (6H, d, CH_3), 2.89 (4H, s, acyclicCH_2CH_2), 3.93 (6H, s, OCH_3), 3.95(6H,s,OCH_3),4.95 (4H, s, OCH_2), 5.92 (2H, s, cyclic S-CH-N), 7.25-7.96 (14H, m, ArH), 8.01 (2H, s, NHCO), 8.34 (2H, s, NH-N)	60.2 60.7	5.14 5.54	6.62 6.74
VIh	$C_{40}H_{42}N_4O_8S_2$	221	770	1.22 (6H,d,CH_3), 2.86 (4H,s,acyclicCH_2CH_2), 3.95 (6H,s,OCH_3), 4.20 (2H, q, cyclic$CHCH_3$),4.94(4H,s,OCH_2),5.92(2H,s,cyclic-S-CH-N), 7.25-7.96 (16H,m,ArH), 8.34(2H,s,NH-N),	65.3 65.5	4.78 4.98	6.60 6.65

VIi	$C_{38}H_{38}N_4O_8S_2$	214	742	1.22 (6H,d,CH_3), 2.81 (4H,s,acyclicCH_2CH_2), 4.20 (2H,q,cyclic $CHCH_3$) 4.90(4H,s,OCH_2), 5.95 (2H,s,cyclic-S-CH-N), 7.25-7.96(16H,m,ArH), 8.34 (2H,s,NH-N), 12.12 (2H,s,ArOH)	60.83 61.4	4.95 5.12	7.12 7.54
VIj	$C_{38}H_{38}N_4O_8S_2$	223	742	1.22 (6H,d,CH_3), 2.85 (4H,s,acyclicCH_2CH_2), 4.20 (2H,q,cyclic $CHCH_3$) 4.94 (4H,s,OCH_2), 5.95 (2H, s, cyclic-S-CH-N), 7.25-7.53 (16H,m,ArH), , 8.34 (2H, s, NH-N), 11.69 (2H,s,ArOH)	60.83 61.3	4.95 5.10	7.12 7.53
VIk	$C_{38}H_{36}N_4O_6S_2Cl_2$	220	778	1.22(6H,d,CH_3), 2.89 (4H,s,acyclicCH_2CH_2), 4.20 (2H,q,cyclic $CHCH_3$) 7.25-7.97 (16H,m,ArH), 4.97 (4H,s,OCH_2), 8.34(2H,s,NH-N), 5.95 (2H,s,cyclic-S-CH-N)	61.59 61.62	4.66 4.86	7.48 7.56
VIl	$C_{38}H_{36}N_6O_{10}S_s$	228	800	1.22 (6H,d,CH_3), 2.89 (4H,s,acyclicCH_2CH_2), 4.20 (2H,q,cyclic $CHCH_3$), 4.95 (4H,s,OCH_2), 5.92 (2H,s,cyclic-S-CH-N), 7.25-7.96(16H,m,ArH), 8.34 (2H,s,NH-N)	56.7 57	4.1 4.5	10.1 10.5

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