

Synthesis and Fungicidal Activity of Bioactive 4,4'-bis[4''-(N-Benzylidinyllamine)-3''-mercapto-1'',2'',4''-triazole-5''-yl methoxy]dibenzyl

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The reaction of 4,4'-diamino dibenzyl (**I**) with sodium nitrite and HCl at 0-5 °C followed by hydrolysis gave 4,4'-dihydroxy dibenzyl (**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)dibenzyl (**IV**) which on condensation with CS₂ and KOH gave 4,4'-bis-[(3''-mercapto-1'',2'',4''-oxadiazole-5''-yl)methoxy]dibenzyl (**V**). Compound **V** further condensed with hydrazine hydrate and yielded 4,4'-bis[4''-amino-3''-mercapto-1'',2'',4''-triazole-5''-yl methoxy]dibenzyl (**VI**). It on condensation with different carbonyl compounds gave 4,4'-bis[4''-(N-benzylidinyllamine)-3''-mercapto-1'',2'',4''-triazole-5''-yl methoxy]dibenzyl (**VIIa-h**). Compounds (**VIIa-h**) were evaluated *in vitro* for their fungi toxicities against *Aspergillus niger* and *Fusarium oxysporum*.

Keywords: Dibenzyl, Triazole, Fungitoxicities, *Aspergillus niger*, *Fusarium oxysporum*.

INTRODUCTION

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 this, one may very well understand the importance of fungitoxic chemicals in agriculture as well as in industry. Literature survey on bryophytes have 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 dibenzyls *viz.*, lunularic acid and lunularin and bis dibenzyl *viz.* plagiocchin, marchatia, *etc.* It has been found that natural as well as synthetic dibenzyls both show antifungal activity [1]. Dibenzyl are the important natural products and have attracted considerable interests due to their biological activities [2]. The occurrence of the dibenzyls in nature in limited amount in rather inaccessible plant species has increased the need for good synthetic methods.

Nitrogen heterocyclic compounds containing 1,2,4-triazole nucleus [3,4], hydrazine and benzylidene derivatives [5] possess various biological activities. 4,4'-dihydroxy dibenzyl (**3**) incorporating 1,2,4-triazole moieties have been relatively less studied. Prompted by these observation we undertook the synthesis of some dibenzyl having 1,2,4-triazole moieties. In

continuation of our research [6-13] work we synthesized new dibenzyl incorporating 1,2,4-triazole moieties.

EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected. ¹H NMR were recorded by using DMSO-*d*₆ on a Bruker DRX-300 (300 MHz FT NMR) spectrometer using TMS as internal reference.

4,4'-Dihydroxy dibenzyl (II): A mixture of cooled solution of 4,4'-diamino dibenzyl (**I**) [13] (0.1 mol) in 2 mol of concentrated hydrochloric acid and 23 mL of water was added drop-wise with stirring in a solution of 0.3 mol of sodium nitrite in water. The solution was stirred for 20 min. The cold solution was added drop-wise to the top of a tube through which a vigorous stream of steam was passed. The resulting mixture, collected at the bottom of the tube, was heated to boiling, cooled and filtered with suction. The synthesized compound agreed well with the analytical data already reported in the literature [14].

4,4'-Ethylenebisphenoxyacetic acid (III): To a solution of 0.03 mol of 4,4'-dihydroxy dibenzyl (**II**) in dry acetone (25 mL), anhydrous K₂CO₃ (10 g) 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 (**III**) was filtered, dried and crystallized from ethanol, (yield 65 %), m.p. 260 °C;

$\nu_{\max}$ 1680 cm^{-1} (C=O), 1030 cm^{-1} (-C-O-C-). m.f.: $\text{C}_{18}\text{H}_{18}\text{O}_6$; m/z 330; ^1H NMR (δ , ppm) 2.5 (2H, s, COOH), 2.82 (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 4.94 (4H, s, OCH_2), 7.1-7.9 (8H, m, ArH).

4,4'-Bis(methoxycarbohydrazide)dibenzyl (IV): A mixture of 4,4'-ethylenebisphenoxyacetic acid (III) (0.05 mol) and hydrazine hydrate (0.06 mol) in absolute ethanol (25 mL) was refluxed on a steam-bath. After refluxing for 4 h excess of ethanol distilled, the solid mass thus obtained are filtered, dried and recrystallized from ethanol (59 %), m.p. 100 °C; $\nu_{\max}$ 3300-3100 (NH-NH), 1650 (CONH), 1055-1256 cm^{-1} (-C-O-C-). m.f.: $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_4$; m/z 358; ^1H NMR (δ , ppm): 2.81 (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 4.65-5.25 (4H, s, NH_2), 4.94 (4H, s, OCH_2), 7.1-7.9 (8H, m, ArH), 8.1 (2H, s, NHCO).

4,4'-Bis[3''-mercapto-1'',2'',4''-oxadiazole]-5''-ylmethoxy]dibenzyl (V): To a solution of 4,4'-bis(methoxycarbohydrazide)dibenzyl (IV) (0.01 mol) in ethanol (20 mL), KOH (0.5 g) in water (5 mL) and CS_2 (0.03 mol) were added. The reaction mixture was refluxed till evolution of H_2S ceased. Thereafter, it was cooled, diluted with cold water (30 mL) and acidified with glacial acetic acid. The solid separated was washed with water and crystallized from ethanol (70 %), m.p. 120 °C. $\nu_{\max}$ 1525 (C=N), 1050 and 1260 (-C-O-C-). m.f.: $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_4\text{S}_2$; m/z 442; ^1H NMR (δ , ppm): 2.50 (2H, s, SH), 2.81, (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 4.94 (4H, s, OCH_2), 7.1-7.9 (8H, m, ArH).

4,4'-Bis[4''-(N-benzylidinylamino)-3''-mercapto-1'',2'',4''-triazol-5''-ylmethoxy]dibenzyl (VI): A mixture of compound V (0.01 mol) and hydrazine hydrate (0.01 mol) in dry pyridine (15 mL) was refluxed for 2 h. The reaction mixture was then neutralized with dil. HCl under cooling. The solid (VI) obtained was crystallized from DMF (72 %), m.p. 146 °C; $\nu_{\max}$ 3225 (NH_2), 2575 (SH), 1570 (C=N), 1045 and 1250 (-C-O-C-). m.f.: $\text{C}_{20}\text{H}_{22}\text{N}_8\text{O}_4\text{S}_2$; m/z 470; ^1H NMR (δ , ppm): 2.50 (2H, s, SH), 2.81 (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 4.94 (4H, s, OCH_2), 5.72 (4H, s, NH_2), 7.1-7.9 (8H, m, ArH), CO).

4,4'-Bis[4''-(N-benzylidinylamino)-3''-mercapto-1'',2'',4''-triazol-5''-ylmethoxy]dibenzyl (VIIa-h): A solution of compound VI (0.01 mol) in glacial acetic acid (20 mL) and

benzaldehyde (0.01 mol) was refluxed for 20 min. The reaction mixture was then cooled, diluted with water and the resulting solid was washed with water and crystallized from ethanol (70 %), m.p. 65 °C. $\nu_{\max}$ 2565 (SH), 1670-1680 (C=N), 1600-1500 (C=C). Similarly compounds VIIa-h were synthesized from VI by a similar procedure (Scheme-I).

VIIa: m.f.: $\text{C}_{34}\text{H}_{30}\text{N}_8\text{O}_2\text{S}_2$; m.p.: 65 °C; m/z 646; ^1H NMR (δ , ppm): 2.50 (2H, s, SH), 2.82, (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 3.34 (4H, s, Ar- OCH_2), 5.06 (2H, s, N=CH), 7.1-7.9 (18H, m, ArH)

VIIb: m.f.: $\text{C}_{34}\text{H}_{30}\text{N}_8\text{O}_4\text{S}_2$; m.p.: 105 °C; m/z 678; ^1H NMR (δ , ppm): 2.50 (2H, s, SH), 2.82, (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 3.34 (4H, s, Ar- OCH_2), 5.06 (2H, s, N=CHAr), 7.12-7.83 (16H, m, ArH), 12.01 (2H, s, ArOH)

VIIc: m.f.: $\text{C}_{36}\text{H}_{34}\text{N}_8\text{O}_4\text{S}_2$; m.p.: 167 °C; m/z 706; ^1H NMR (δ , ppm): 2.50 (s, 2H, SH), 2.82, (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 3.34 (s, 4H, Ar- OCH_2), 4.85 (s, 4H, OCH_3), 5.09 (2H, N=CHAr), 7.12-7.83 (16H, m, ArH), 12.01 (2H, s, ArOH).

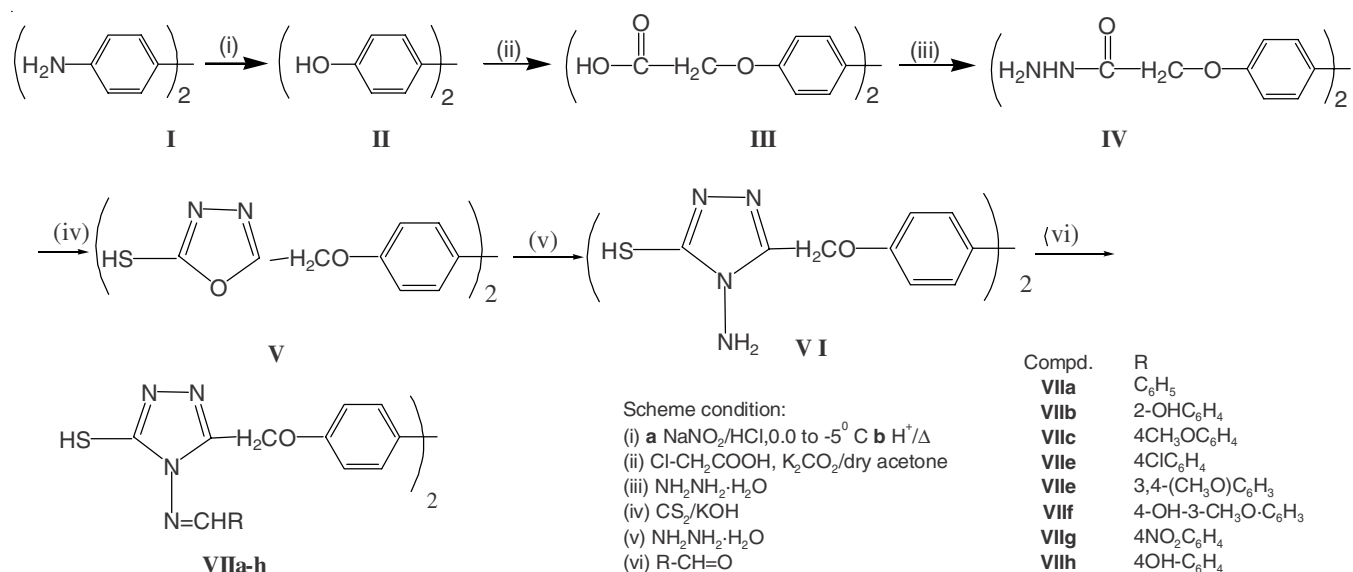
VIIId: m.f.: $\text{C}_{34}\text{H}_{28}\text{N}_8\text{O}_2\text{S}_2\text{Cl}_2$; m.p.: 205 °C; m/z 714; ^1H NMR (δ , ppm): 2.50 (2H, s, SH), 2.82, (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 3.34 (4H, s, Ar- OCH_2), 5.05 (2H, s, N=CHAr), 7.17-7.63 (16H, m, ArH)

VIIe: m.f.: $\text{C}_{38}\text{H}_{38}\text{N}_8\text{O}_6\text{S}_2$; m.p.: 180 °C; m/z 766; ^1H NMR (δ , ppm): 2.50 (2H, s, SH), 2.82, (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 3.34 (s, 4H, Ar- OCH_2), 3.39 (6H, s, OCH_3), 3.95 (6H, S, OCH_3), 5.06 (2H, s, N=CHAr) 7.21-7.63 (14H, m, ArH)

VIIIf: m.f.: $\text{C}_{36}\text{H}_{34}\text{N}_8\text{O}_6\text{S}_2$; m.p.: 135 °C; m/z 738; ^1H NMR (δ , ppm): 2.50 (2H, s, SH), 2.82, (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 3.34 (4H, s, Ar- OCH_2) 3.95 (6H, S, OCH_3), 5.06 (2H, s, N=CHAr), 7.12-7.83 (14H, m, ArH), 11.69 (2H, s, ArOH).

VIIg: m.f.: $\text{C}_{34}\text{H}_{28}\text{N}_{10}\text{O}_3\text{S}_2$; m.p.: 190 °C; m/z 640; ^1H NMR (δ , ppm): 2.50 (2H, s, SH), 2.82, (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 3.34 (4H, s, Ar- OCH_2), 5.06 (2H, s, N=CHAr), 7.12-7.83 (16H, m, ArH)

VIIh: m.f.: $\text{C}_{34}\text{H}_{30}\text{N}_8\text{O}_4\text{S}_2$; m.p.: 220 °C; m/z 678; ^1H NMR (δ , ppm): 2.82, (4H, s, acyclic $\text{CH}_2\text{-CH}_2$), 2.50 (2H, s, SH), 3.34 (s, 4H, s, Ar- OCH_2) 5.06 (2H, s, N=CHAr), 7.12-7.83 (14H, m, ArH), 11.69 (2H, s, ArOH).



Scheme-I

RESULTS AND DISCUSSION

The refluxing of 4,4'-ethylenebisphenol(4,4'-dihydroxy dibenzyl) 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)dibenzyl **IV**. Compound **IV** on treatment with CS₂ and KOH gave 4,4'-bis[3''-mercapto-1'',2'',4''-oxadiazole)-5''-yl methoxy]dibenzyl (**V**), which is again treated with hydrazine hydrate gave 4,4'-bis(4''amino-3''-mercapto-1'',2'',4''-triazole-5''-yl methoxy) dibenzyl (**VI**). Compound **VI** on cyclocondensation with different aromatic aldehyde gave 4,4'-bis[4''-(N-benzylidinyllamino)-3''-mercapto-1'',2'',4''-triazol-5''-ylmethoxy]dibenzyl (**VIIa-h**).

Compounds **V**, **VI** and **VIIa-h** 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 was also tested under similar condition for comparing the results. Among the tested compounds **VIIc**, **VIIId** and **VIIe** were found to be most active against both the test fungus (Table-1).

TABLE-1
ANTIFUNGAL SCREENING RESULTS OF
COMPOUNDS **VIII**, **IX** AND **Xa-e**

Compd.	<i>Aspergillus niger</i>			<i>Fusarium oxysporum</i>		
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
V	47	32	13	51	29	15
VI	64	50	24	61	33	20
VIIa	78	52	32	67	50	27
VIIb	73	47	21	69	34	12
VIIc	100	67	53	100	74	51
VIIId	93	61	38	87	69	32
VIIe	89	72	29	83	64	22
VIIIf	68	44	12	70	49	18
VIIg	72	50	23	74	52	28
VIIh	63	47	20	65	48	30

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