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### Synthesis and antibacterial evaluation of some novel aminothiazole derivatives

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#### ABSTRACT

A series of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-carboxylic acid- (4-phenyl/ substituted phenyl thiazole)-amide (VI a-g) were prepared. The structures of aminothiazole derivatives were confirmed on the basis of spectral data. The newly synthesized title compounds were screened for their *in vitro* antibacterial activity. Some of the compounds exhibited encouraging results.

**Keywords:** 4-aryl-2-aminothiazoles, 4'-Bromomethylbiphenyl-2-carbonitrile, 2-n-butyl-4-chloro-5-hydroxymethyl imidazole (II), Antimicrobial activity.

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#### INTRODUCTION

The discovery of first potent orally active nonpeptide A II antagonist, Losartan has stimulated extensive research interest in this area, and numerous derivatives have been reported as potent and selective antagonists (1, 2). The great majority of them contain biphenyl moiety. Thiazole and imidazole derivatives are an important class of heterocyclic compounds. They occupy an important position in medicinal chemistry, presenting a wide range of bioactivities. As medicines, many of them display including antibacterial and antifungal (3, 4), anti-HIV (5), hypertension (6), anti-inflammatory (7), anticancer (8), anti-convulsant (9), antidepressant antitubercular activities (10). Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities. Thiazole, particularly the 2-amino thiazole nucleus have been incorporated into a wide variety of therapeutically interesting candidates. On the other hand, Imidazole is a vital heterocyclic nucleus which is well known for its wide biological profile. Imidazole derivatives are associated with a wide array of pharmacological activities including antimicrobial (11-12), anti-inflammatory and analgesic (13-14), antitubercular (15), antiviral (16).

The approach to the preparation of potential biologically active compounds today is predominantly based on the combination of different substructures which increased the biological activity of known active substances. The reason for one such synthesis in this study is based on the fact that, combining biphenylimidazole with substituted 2-aminothiazole by  $-\text{CONH}_2$ - moiety is expected to give novel heterocyclic compounds with better biological activities. Up till now, the antibacterial activities of these compounds have not been reported. In this paper, we described the synthesis of the compounds which possess both biphenylimidazole and 2-aminothiazole moieties and are evaluated for its antibacterial activities.

The approach to the preparation of potential biologically active compounds and in continuation of our ongoing studies on novel biologically active molecules, we have designed and synthesized some novel 2-aminothiazoles derivatives as described in Scheme-1 and evaluated for its antibacterial activities.

## MATERIALS AND METHODS

### Experimental

All melting points were determined using a manual Buchi electro thermal apparatus (range 0–300 °C) in glass capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT IR 1600. NMR spectra were recorded on a Bruker-400 MHz spectrometer and are expressed in a using TMS as internal reference. 4'-Bromomethylbiphenyl-2-carbonitrile (III) and 2-n-butyl-4-chloro-5-hydroxymethyl imidazole (II) are commercial reagents. Substituted aryl-2-aminothiazoles (Ia-Ig) were synthesized according to the literature (17-18). All the reactions were monitored by thin layer chromatography over pre-coated silica gel plates, using UV lamp, iodine vapours or  $\text{KMnO}_4$  spray as developing agents. The purification was carried out by using 60-120 mesh silica gel by column chromatography (obtained from Spectrochem) with a suitable eluting system such as Hexane, Ethyl acetate, Chloroform, Chloroform:Methanol::9:1.

### Synthesis of 2-n-Butyl-4-chloro-1[(2'-cyanobiphenyl-4-yl)methyl]-5- hydroxyl-methyl imidazole(IV).<sup>(19)</sup>

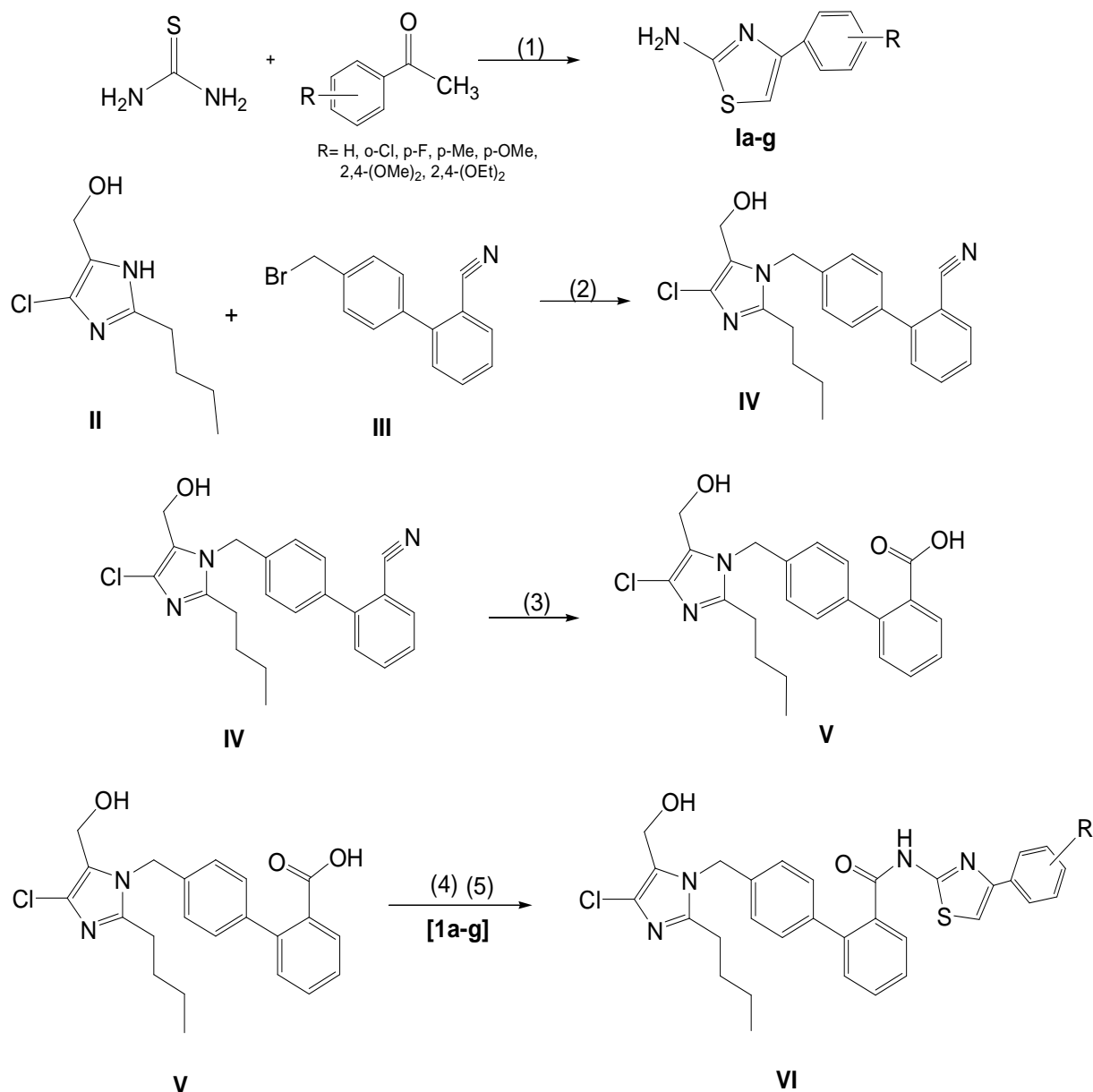
7.44 gm (24.77mmol) of Sodium methoxide and 100ml of DMF was suspended in a 1L flask and flask was cooled to 10°C. 25.99 gm (25.69mmol) of 2-n-butyl-4-chloro-5-hydroxymethyl imidazole was dissolved in 100ml of DMF separately and then added to reaction mixture drop wise at cooled condition during 30 mins and continued stirring at RT for another 30 mins. Then added solution of 25.00 gm (22.94mmol) of 4-bromomethyl-2'-cyanobiphenyl in 100ml of DMF to reaction mixture drop wise during 30 mins and continued stirring at RT for overnight. Reaction was monitored by TLC (System: Chloroform: methanol:: 9:1). The RM was poured into ice water. The gummy residue obtained was extracted by ethyl acetate (150mlX3). The ethyl acetate layer was washed with hot water, dried and evaporated. Then semisolid residue was obtained and it was dissolved in toluene by heating and allowed to attain room temperature and kept in cold condition. The solid was crystallized, filtered and dried. Yield: 8.0gm (23%), LC-MS: m/z 379 [M+].

### Synthesis of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-carboxylic acid 2-n-Butyl-4-chloro-1-[[2'-cyanobiphenyl-4-yl]-methyl]-5hydroxymethyl imidazole [III].

8gm of 2-n-Butyl-4-chloro-1[(2'-cyanobiphenyl-4-yl)methyl]-5- hydroxyl-methyl imidazole (21.06 mmol), 50% KOH Solution (100ml) and Ethanol (200ml) were heated to reflux at

78°C for about 24hrs. The reaction was monitored by TLC (CHCl<sub>3</sub>: MeOH:: 9:1).The reaction mixture was evaporated to dryness and the residue was dissolved in water and washed with diethyl ether. The aqueous layer was acidified by using dil.HCl to pH 3. Then semisolid residue was extracted and then dried over Na<sub>2</sub>SO<sub>4</sub> and solvent was evaporated. The crude was purified by column chromatography using Chloroform: Methanol:: 9:1. Yield: 4.2gm (50%), LC-MS: m/z 399 [M+].

### Scheme 1



Reagents;(1)I<sub>2</sub>, Reflux,5hr (2) Sodium methoxide,DMF,RT,18hrs.,35%; (3)Ethanol, 50% KOH Solution, Reflux,24hrs.,50% ;(4)(COCl)<sub>2</sub>,DCM,Reflux,30mts.; (5)TEA,Acetonitrile,RT,18hrs, 40%.

### General Procedure for preparation of Amide Bond Formation. (VI a-g)

4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-carboxylic acid (2.1gm, 5.27 mmol) was dissolved in 50 ml of Dichloromethane at cold condition and (0.98gm, 5.38 mmol) oxalyl chloride was added drop wise and then heated to reflux for about 30 mins. The reaction was monitoring by TLC. The reaction mixture was evaporated

and added 50ml of dichloromethane and evaporated to get acid chloride. The residue was dissolved in 10ml of Acetonitrile and added to the solution of substituted 4-Phenyl-2-aminothiazole (1.10gm, 4.8mmol) and Triethylamine (1.5gm 15mmol) in 10ml of Acetonitrile drop wise at room temperature and continued stirring for overnight. The solvent was evaporated and purified by purified by column chromatography.

**Synthesis of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-carboxylic acid- (4-phenylthiazole)-amide**

Yield: 75% ; IR(KBr): 3295, 3176, 2956, 2927, 2829, 1655, 1533  $\text{Cm}^{-1}$ ,  $^1\text{H NMR}(\text{CDCl}_3)$ :  $\delta$  0.86-0.90 (3H, t,  $\text{CH}_3$ -);  $\delta$  1.25-1.27 (2H, m,  $-\text{CH}_2$ -);  $\delta$  1.46-1.48 (2H, m,  $-\text{CH}_2$ -);  $\delta$  2.50-2.57 (2H, m,  $-\text{N}=\text{C}-\text{CH}_2$ -);  $\delta$  4.25-4.28 (2H, s,  $-\text{CH}_2\text{-OH}$ );  $\delta$  4.90 (H, b,  $-\text{OH}$ );  $\delta$  5.12-5.14 (2H, s,  $-\text{CH}_2\text{-Ar}$ );  $\delta$  6.68-6.71 (H, s,  $-\text{HC}=\text{C}$ ); 6.991-7.697 (13H, m, Ar);  $\delta$  8.021 (H, s,  $-\text{CO-NH}$ -). Anal. Calcd for  $\text{C}_{31}\text{H}_{29}\text{ClN}_4\text{O}_2\text{S}$ : C, 66.83; H, 5.25; N, 10.06%. Found: C, 66.51; H, 5.15; N, 9.96%

**Synthesis of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-carboxylic acid- 4(2-chlorophenylthiazole)-amide (VI b)**

Yield: 65% ; IR(KBr): 3285, 3176, 2946, 2927, 2829, 1655, 1583, 1200-1000  $\text{Cm}^{-1}$ ,  $^1\text{H NMR}(\text{CDCl}_3)$ :  $\delta$  0.86-0.92 (3H, t,  $\text{CH}_3$ -);  $\delta$  1.26-1.28 (2H, m,  $-\text{CH}_2$ -);  $\delta$  1.46-1.48 (2H, m,  $-\text{CH}_2$ -);  $\delta$  2.53-2.57 (2H, m,  $-\text{N}=\text{C}-\text{CH}_2$ -);  $\delta$  4.26-4.29 (2H, s,  $-\text{CH}_2\text{-OH}$ );  $\delta$  4.96 (H, b,  $-\text{OH}$ );  $\delta$  5.14-5.16 (2H, s,  $-\text{CH}_2\text{-Ar}$ );  $\delta$  6.70-6.73 (2H, s,  $-\text{HC}=\text{C}$ ); 6.66-7.70 (12H, m, Ar);  $\delta$  8.08 (H, s,  $-\text{CO-NH}$ -). Anal. Calcd for  $\text{C}_{31}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_2\text{S}$ : C, 62.94; H, 4.77; N, 9.47%. Found: C, 62.66; H, 4.86; N, 9.27%.

**Synthesis of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-carboxylic acid- 4(4-fluorophenylthiazole)-amide (VI c)**

Yield: 78% ; IR(KBr): 3298, 3176, 2946, 2927, 2829, 1678, 1583, 1200-1000  $\text{Cm}^{-1}$ ,  $^1\text{H NMR}(\text{CDCl}_3)$ :  $\delta$  0.84-0.91 (3H, t,  $\text{CH}_3$ -);  $\delta$  1.23-1.28 (2H, m,  $-\text{CH}_2$ -);  $\delta$  1.39-1.44 (2H, m,  $-\text{CH}_2$ -);  $\delta$  2.54-2.58 (2H, m,  $-\text{N}=\text{C}-\text{CH}_2$ -);  $\delta$  4.26-4.29 (2H, s,  $-\text{CH}_2\text{-OH}$ );  $\delta$  5.0 (H, b,  $-\text{OH}$ );  $\delta$  5.18-5.20 (2H, s,  $-\text{CH}_2\text{-Ar}$ );  $\delta$  6.71-6.74 (H, s,  $-\text{HC}=\text{C}$ ); 6.69-7.72 (12H, m, Ar);  $\delta$  8.0 (H, s,  $-\text{CO-NH}$ -). Anal. Calcd for  $\text{C}_{31}\text{H}_{28}\text{ClFN}_4\text{O}_2\text{S}$ : C, 64.74; H, 4.91; N, 9.74%. Found: C, 64.34; H, 4.78; N, 9.54%.

**Synthesis of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-carboxylic acid- 4(4-methylphenylthiazole)-amide (VI d)**

Yield: 72% ; IR(KBr): 3295, 3176, 2946, 2927, 2829, 1655, 1000  $\text{Cm}^{-1}$ ,  $^1\text{H NMR}(\text{CDCl}_3)$ :  $\delta$  0.84-0.89 (3H, t,  $\text{CH}_3$ -);  $\delta$  1.24-1.27 (2H, m,  $-\text{CH}_2$ -);  $\delta$  1.44-1.49 (2H, m,  $-\text{CH}_2$ -);  $\delta$  2.49-2.54 (2H, m,  $-\text{N}=\text{C}-\text{CH}_2$ -);  $\delta$  2.12-2.18 (3H, s, Ar- $\text{CH}_3$ );  $\delta$  4.28-4.30 (2H, s,  $-\text{CH}_2\text{-OH}$ );  $\delta$  4.95 (H, b,  $-\text{OH}$ );  $\delta$  5.10-5.12 (2H, s,  $-\text{CH}_2\text{-Ar}$ );  $\delta$  6.65-6.70 (H, s,  $-\text{HC}=\text{C}$ ); 6.991-7.697 (13H, m, Ar);  $\delta$  8.021 (H, s,  $-\text{CO-NH}$ -). Anal. Calcd for  $\text{C}_{32}\text{H}_{31}\text{ClN}_4\text{O}_2\text{S}$ : C, 67.29; H, 5.47; N, 9.81%. Found: C, 66.89; H, 5.37; N, 9.51.

**Synthesis of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-carboxylic acid- 4(4-methoxyphenylthiazole)-amide (VI e)**

Yield: 60% ; IR(KBr): 3295, 3176, 2946, 2927, 2829, 1682, 1600  $\text{Cm}^{-1}$ ,  $^1\text{H NMR}(\text{CDCl}_3)$ :  $\delta$  0.86-0.92 (3H, t,  $\text{CH}_3$ -);  $\delta$  1.26-1.28 (2H, m,  $-\text{CH}_2$ -);  $\delta$  1.46-1.48 (2H, m,  $-\text{CH}_2$ -);  $\delta$  2.53-2.57 (2H, m,  $-\text{N}=\text{C}-\text{CH}_2$ -);  $\delta$  3.52-3.58 (3H, s, Ar- $\text{OCH}_3$ );  $\delta$  4.26-4.29 (2H, s,  $-\text{CH}_2\text{-OH}$ );  $\delta$  4.96 (H, b,  $-\text{OH}$ );  $\delta$  5.14-5.16 (2H, s,  $-\text{CH}_2\text{-Ar}$ );  $\delta$  6.70-6.73 (H, s,  $-\text{HC}=\text{C}$ ); 6.66-7.70 (12H, m, Ar);  $\delta$  8.08 (H, s,  $-\text{CO-NH}$ -). Anal. Calcd for  $\text{C}_{32}\text{H}_{31}\text{ClN}_4\text{O}_3\text{S}$ : C, 65.46; H, 5.32; N, 9.54%. Found: C, 65.16; H, 5.25; N, 9.34.

**Synthesis of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-carboxylic acid- 4(2,4-dimethoxyphenylthiazole)-amide (VI f)**

Yield: 58% ; IR(KBr): 3295, 3176, 2946, 2927, 2829, 1685, 1610  $\text{Cm}^{-1}$ ,  $^1\text{H NMR}(\text{CDCl}_3)$ :  $\delta$  0.92-0.94 (3H, t,  $\text{CH}_3$ -);  $\delta$  1.28-1.32 (2H, m,  $-\text{CH}_2$ -);  $\delta$  1.48-1.50 (2H, m,  $\text{CH}_2$ -);  $\delta$  2.54-2.58 (2H, m,  $-\text{N}=\text{C}-\text{CH}_2$ -);  $\delta$  3.58-3.68 (6H, s,  $\text{Ar}-(\text{OCH}_3)_2$ );  $\delta$  4.26-4.29 (2H, s,  $-\text{CH}_2$ -OH);  $\delta$  4.96 (H, b, -OH);  $\delta$  5.13-5.17 (2H, s,  $-\text{N}-\text{CH}_2$ -Ar);  $\delta$  6.69-6.75 (H, s,  $-\text{HC}=\text{C}$ ); 6.71-7.80 (12H, m, Ar);  $\delta$  8.12 (H, s,  $-\text{CO}-\text{NH}$ -). Anal. Calcd for  $\text{C}_{33}\text{H}_{33}\text{ClN}_4\text{O}_4\text{S}$ : C, 64.22; H, 5.39; N, 9.08. Found: C, 63.87; H, 5.09; N, 8.76.

**Synthesis of 4'-(2-n-Butyl-4-chloro-5-hydroxymethyl-imidazol-1-yl-methyl-biphenyl-2-carboxylic acid- 4(2,4-diethoxyphenylthiazole)-amide (VI g)**

Yield: 50%; IR(KBr): 3295, 3176, 2946, 2927, 2829, 1685, 1695  $\text{Cm}^{-1}$ ,  $^1\text{H NMR}(\text{CDCl}_3)$ :  $\delta$  0.86-0.92 (3H, t,  $\text{CH}_3$ -);  $\delta$  1.24-1.38 (5H, m,  $-\text{CH}_2$ - &  $\text{CH}_3$ );  $\delta$  1.46-1.48 (2H, m,  $\text{CH}_2$ -);  $\delta$  2.53-2.57 (2H, m,  $-\text{N}=\text{C}-\text{CH}_2$ -);  $\delta$  3.62-3.68 (3H, m,  $\text{Ar}-(\text{OCH}_2)_2$ -);  $\delta$  4.26-4.29 (2H, s,  $-\text{CH}_2$ -OH);  $\delta$  4.96 (H, b, -OH);  $\delta$  5.14-5.16 (2H, s,  $-\text{N}-\text{CH}_2$ -Ar);  $\delta$  6.70-6.73 (H, s,  $-\text{HC}=\text{C}$ ); 6.66-7.70 (12H, m, Ar);  $\delta$  8.08 (H, s,  $-\text{CO}-\text{NH}$ -). Anal. Calcd for  $\text{C}_{35}\text{H}_{37}\text{ClN}_4\text{O}_4\text{S}$ : C, 65.15; H, 5.78; N, 8.68. Found: C, 64.75; H, 5.65; N, 8.52.

**Antimicrobial Activity**

Compounds **V a-g** were screened for their in-vitro antibacterial activity against *S.aureus* and *B. subtilis* employing cup-plate method at the concentration of 100 $\mu\text{g/ml}$  in nutrient agar media[20-22] and also for in-vitro antifungal activity against *C. albicans* and *A. Niger* by cup plate method at 100 $\mu\text{g/ml}$ . concentration using sabouraud-dextrose agar. DMSO was used as solvent control for antimicrobial activity. Streptomycin and Griesuofulin were used as standard for antibacterial and antifungal activities respectively. The area of inhibition of zone measured in cm. The results are listed in Table-1.

**Table-1. Antimicrobial and Antifungal Data of compounds**

Compounds	Antibacterial		Antifungal	
	<i>S.aureus</i>	<i>B.subtilis</i>	<i>C.albicans</i>	<i>A.niger</i>
VI a	09	10	07	10
VI b	12	11	08	11
VI c	13	14	10	13
VI d	09	10	10	10
VI e	13	13	12	12
VI f	14	15	11	13
VI g	16	17	12	11
IV	09	08	07	08
Streptomycin	24	26	-	-
Griesofulvin	-	-	20	22

**RESULTS AND DISCUSSION**

From the antimicrobial screening it was observed that all the compounds exhibited the activity against all the organisms employed. Looking at the structure activity relationship, marked inhibition in bacteria was observed in the compounds bearing  $\text{R} = \text{Cl}$ ,  $\text{F}$ ,  $p\text{-OCH}_3$ ,  $2,4\text{-(OCH}_3)_2$ ,  $2,4\text{-(OCH}_2\text{CH}_3)_2$  (Vb, Vc, Ve, Vf, Vg) substituents where as other compounds showed moderate to good activity. Fungicidal screening data also revealed that compounds

bearing R=F,-2,4-(OCH<sub>3</sub>)<sub>2</sub>,-2,4-(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> (Vc, Vf, Vg) imparted maximum activity to the compounds, where as other compounds showed moderate to good activity. Further investigation on the biological activity of these compounds is in progress.

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