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Synthesis and Fungicidal Activity of Novel 3-(Substituted/unsubstituted phenylselenonyl)-1-ribosyl/deoxyribosyl-1*H*-1,2,4-triazole

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ABSTRACT: Reaction of potassium 1*H*-1,2,4-triazole-3-selenolate (**I**) with acetylated ribose/deoxyribose (**IIa,b**) in the presence of montmorillonite K 10 as a solid adsorbent furnished potassium 1-acetylated ribosyl/deoxyribosyl-1*H*-1,2,4-triazole-3-selenolate (**IIIa,b**) with excellent yield under microwave irradiation in solvent-free conditions. This eliminates a series of complex isolation procedures and often minimizes the use of a large amount of expensive, toxic, and hazardous solvents after each step. This procedure reduces reaction time and cost and enhances yield. Reaction of compound (**IIIa,b**) with substituted/unsubstituted aryl diazonium chloride (**IVa−e**) at 0−5 °C gave pure 3-(substituted/unsubstituted phenyl selanyl)-1-acetylribosyl/deoxyribosyl-1*H*-1,2,4-triazole (**Va−j**). Oxidation of compound (**Va−j**) with oxone followed by alkaline hydrolysis furnished quantitatively and analytically pure 3-(substituted/unsubstituted phenylselenonyl)-1-ribosyl/deoxyribosyl-1*H*-1,2,4-triazole (**VIIa−j**). Compounds **VIa−j** and **VIIa−j** were evaluated in vitro for their fungitoxicities against *Fusarium oxysporum* and *Penicillium citrinum*. All the compounds were found to be antifungal active. Some of the compounds displayed activities comparable with that of the commercial fungicide Dithane M-45 and griseofulvin. Structure−activity relationships for the screened compounds were discussed. The fact that both of these fungi have developed resistance to several fungicide groups made them optimal candidates as target organisms for ongoing research about the potential application of 1,2,4-triazole and analogue compounds as reduced-risk fungicides.

KEYWORDS: *microwave induced, montmorillonite K 10 clay, 1,2,4-triazole, selenium, fungicidal activity*

INTRODUCTION

Many chemical crop protectants are being used for the management and control of fungal diseases in modern agriculture. Control of fungal diseases is essential to maintain high agricultural productivity and to minimize monetary losses. Further, the agrochemical industry has successfully developed a wide array of fungicides with various chemical structures and modes of action. However, an inevitable problem associated with the use of fungicides is the occurrence of the increased resistance to commercially available agrochemicals as well as the stricter environmental and toxicological regulations now being introduced worldwide, and the need for fungicides to be replaced by safer and more effective agrochemicals with reduced environmental and/or mammalian toxicity remains important.

Over the last few decades, 1,2,4-triazoles and their derivatives have received considerable attention owing to their pesticidal[1] and antifungal[2−4] activities. Representatives of this class of fungicides (Figure 1) are tebuconazole, flutriafol, hexaconazole, and cyproconazole.[5−8]

Selenium is of great interest in biochemistry,[9] chemistry,[10−13] medicine, and medicine-related fields.[14,15] It is also used for bioisosteric replacement of oxygen and sulfur in bioactive molecules to obtain more bioactivity or safety.[16]

The biological and commercial significance of the 1,2,4-triazoles, microelements, and selenium and their challenging molecular architectures have prompted a number of synthetic studies. Our approach for developing efficacious fungicide leads was to design molecules containing the 1,2,4-triazoles, selenium atom, and sugar moiety, and we have synthesized a series of hitherto unknown

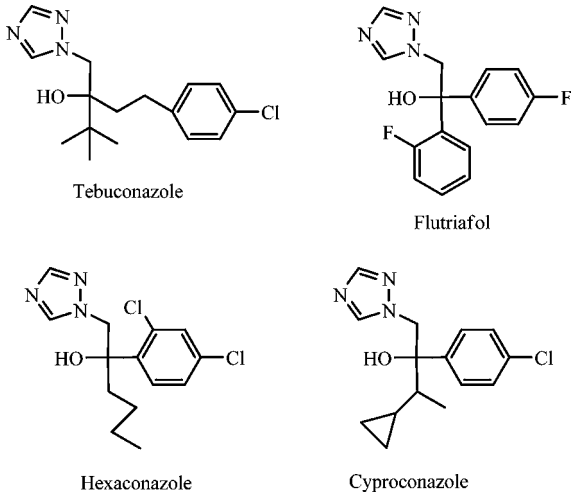

Figure 1. Some representative structures of fungicides.

title compounds, 3-(substituted/unsubstituted phenylselenonyl)-1-ribosyl/deoxyribosyl-1*H*-1,2,4-triazole (**VIIa−j**) (Scheme 1).

Our study[17−21] on structure−activity relationships showed that, sometimes, minor changes in heterocyclic nuclei enhance the biological activity many fold over the parent nuclei. Further

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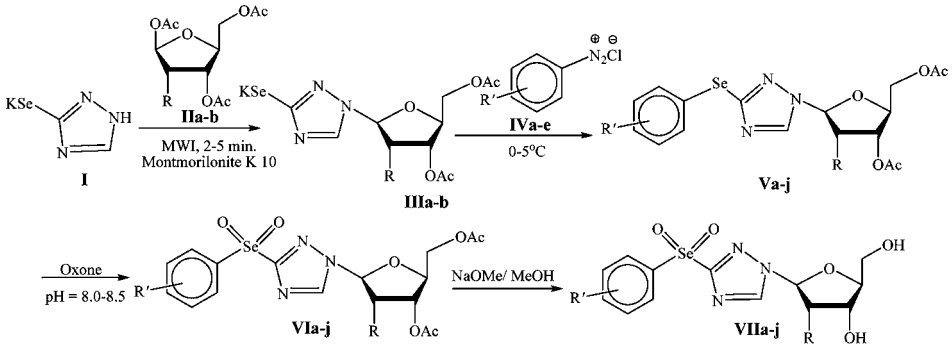
Scheme 1



Compd.	R	R′	Compd.	R	R′
IIIa	-OAc	-	IIIb	H	-
Va, VIa	-OAc	H	VIIa	-OH	H
Vb, VIb	-OAc	4-CH_3O	VIIb	-OH	4-CH_3O
Vc, VIc	-OAc	4-CH_3	VIIc	-OH	4-CH_3
Vd, VId	-OAc	4-Cl-	VIId	-OH	4-Cl
Ve, VIe	-OAc	4-NO_2	VIIe	-OH	4-NO_2
Vf, VIf	H	H	VIIf	H	H
Vg, VIg	H	4-CH_3O	VIIg	H	4-CH_3O
Vh, VIh	H	4-CH_3	VIIh	H	4-CH_3
Vi, VIi	H	4-Cl	VIIi	H	4-Cl
Vj, VIj	H	4-NO_2	VIIj	H	4-NO_2

search for new, effective, and safer nuclei has led to an improvement in the existing drugs by increasing their potency and duration of action and decreasing their toxic effects. Essential to these efforts is the identification of new lead candidates possessing high levels of desirable biological activities, reduced unwanted toxicities, new structural types, and perhaps different modes of action, thereby providing protection from cross-resistance to currently used agrochemicals.

The structural assignments of the synthesized products were based on ^{1}H NMR spectra and mass spectra (Table 1). Compound **IIIa,b** was synthesized under microwave irradiation by the reaction of **I** and **IIa,b** in the presence of montmorillonite K 10 as a solid adsorbent with excellent yield in solvent-free conditions. This procedure often minimizes the use of a large amount of expensive, toxic, and hazardous solvents after each step, reduces reaction time and cost, and enhances yield. Reaction of compound **IIIa,b** with substituted/unsubstituted aryl diazonium chloride **IVa−e** at 0−5 °C gave pure 3-(substituted/unsubstituted phenyl selanyl)-1-acetylribosyl/deoxyribosyl-1*H*-1,2,4-triazole (**Va−j**). Oxidation of compound **Va−j** with oxone followed by alkaline hydrolysis furnished quantitatively and analytically pure 3-(substituted/unsubstituted phenylselenonyl)-1-ribosyl/deoxyribosyl-1*H*-1,2,4-triazole (**VIIa−j**). Of the tested compounds **VIa−j** and **VIIa−j**, compounds **VIIb** and **VIId** displayed in vitro fungitoxicity comparable to that of the commercial fungicide griseofulvin and Dithane M-45 at 1000 μg/mL concentration against *Fusarium oxysporum* and *Penicillium citrinum* (Table 2).

EXPERIMENTAL SECTION

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. Melting points were determined by open glass capillary method and are uncorrected. The structural assignments of the synthesized products were based on elemental analysis (C, H, N), ^{1}H NMR spectra, and mass spectra.^{1}H NMR spectra were recorded on a Bruker (400 MHz) FT spectrometer in $CDCl_3$ using TMS as internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer at 70 eV. Elemental analyses were carried out using a Coleman automatic carbon, hydrogen, and nitrogen analyzer. An unmodified laboratory microwave oven (model BP 310/50) operating at 2450 MHz was used for all the experiments. The final products were purified by column chromatography using silica gel (100 mesh) with increasing percentage of hexane:MeOH. The progress of the reaction was monitored by TLC (Merck silica gel).

Potassium 1-Acetylated Ribosyl/deoxyribosyl-1*H*-1,2,4-triazole-3-selenolate (IIIa,b) (Microwave Irradiation). A mixture of potassium 1*H*-1,2,4-triazole-3-selenolate (**I**)[16,22,23] (2.5 mmol) and acetylated ribose/acetylated deoxyribose (**IIa,b**) (2.5 mmol) was adsorbed on montmorillonite K-10 clay (0.5 mmol) in a 100 mL Pyrex conical flask capped with a funnel and subjected to microwave irradiation for the specified time (Table 1). The completion of the reaction was checked by TLC using hexane:MeOH (7:3 v/v). The reaction mixture was cooled to room temperature (rt) and eluted with acetone (3 × 20 mL). The eluate was evaporated to dryness and washed with $NaHCO_3$ (3.0% w/v) and finally with cold H_2O and dried over anhydrous $MgSO_4$. The residue on purification by silica gel column chromatography (hexane:MeOH; 7:3 v/v) furnished analytically pure **IIIa,b**.

For comparison purpose, the final temperature was recorded immediately after the MW irradiation for 2 min and was found to reach about 90 °C from 27 °C (room temperature). The same reaction was also carried out by using a thermostated water bath at the same bulk of temperature (90 °C) as for the microwave activated method but for a longer (optimized) period of time to ascertain whether the MW method improves the yield or simply increases conversion rates.

3-(Substituted/unsubstituted phenyl selanyl)-1-acetylribosyl/deoxyribosyl-1*H*-1,2,4-triazole (Va−j). A solution of substituted/unsubstituted arylamine (0.05 mol) in 30 mL of methanol was added slowly to 5.0 mL of concentrated HCl. It was stirred for 10 min at room temperature and cooled to −5 °C. A solution of 3.51 g (0.051 mol) of

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Table 1. Physical and Spectral Data of Compounds IVa−b, Va−j, VIa−j, and VIIa−j

compd	mp, °C	yield,[a] % (s)	yield,[b] % (h)	mol formula[c]	M^+, m/z	^{1}H NMR (δ ppm) ($CDCl_3$)
IIIa	230	89 (180)	80 (6.00)	$C_{13}H_{16}KN_3O_7Se$	445	2.21 (9H, s, 3 CH_3CO), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 8.77 (1H, s, N=CH−N)
IIIb	232	90 (200)	82 (7.30)	$C_{11}H_{14}KN_3O_5Se$	387	2.21 (6H, s, 2 CH_3CO), 2.65 (2H, dd, C−CH_2−C), 4.31 (1H, m, −CH−O), 4.34 (2H, d, $-CH_2-O$), 5.42 (1H, m, −CH−O), 5.95 (1H, t, O−CH−N), 8.77 (1H, s, N=CH−N)
Va	240		85 (7.00)	$C_{19}H_{21}N_3O_7Se$	483	2.21 (9H, s, 3 CH_3CO), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.44−7.47 (5H, m, ArH), 8.77 (1H, s, N=CH−N)
Vb	256		87 (7.30)	$C_{20}H_{23}N_3O_8Se$	513	2.21 (9H, s, 3 CH_3CO), 3.83 (3H, s, CH_3O), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 6.99−7.33 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
Vc	265		89 (7.45)	$C_{20}H_{23}N_3O_7Se$	497	2.21 (9H, s, 3 CH_3CO), 2.34 (3H, s, CH_3), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.32−7.43 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
Vd	276		85 (7.00)	$C_{19}H_{20}ClN_3O_7Se$	517	2.21 (9H, s, 3 CH_3CO), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.38−7.49 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
Ve	287		82 (8.00)	$C_{19}H_{20}N_4O_9Se$	528	2.21 (9H, s, 3 CH_3CO), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.70−8.26 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
Vf	286		82 (7.15)	$C_{17}H_{19}N_3O_5Se$	425	2.21 (6H, s, 2 CH_3CO), 2.65 (2H, dd, C−CH_2−C), 4.34 (2H, d, $-CH_2-O$), 4.31 (1H, m, CH−O), 5.42 (1H, m, −CH−O), 5.95 (1H, t, O−CH−N), 7.45−8.51 (5H, m, ArH), 8.77 (1H, s, N=CH−N)
Vg	287		85 (7.30)	$C_{18}H_{21}N_3O_6Se$	455	2.21 (6H, s, 2 CH_3CO), 2.65 (2H, dd, C−CH_2−C), 3.83 (3H, s, CH_3O), 4.31 (1H, m, CH−O), 4.34 (2H, d, $-CH_2-O$), 5.42 (1H, m, −CH−O), 5.95 (1H, t, O−CH−N), 7.45−8.51 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
Vh	265		89 (8.00)	$C_{18}H_{21}N_3O_5Se$	439	2.21 (6H, s, 2 CH_3CO), 2.34 (3H, s, CH_3), 2.65 (2H, dd, C−CH_2−C), 4.31 (1H, m, CH−O), 4.34 (2H, d, $-CH_2-O$), 5.42 (1H, m, −CH−O), 5.95 (1H, t, O−CH−N), 7.32−7.41 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
Vi	265		84 (7.15)	$C_{17}H_{18}ClN_3O_5Se$	459	2.21 (6H, s, 2 CH_3CO), 2.65 (2H, dd, C−CH_2−C), 4.31 (1H, m, CH−O), 4.34 (2H, d, $-CH_2-O$), 5.42 (1H, m, −CH−O), 5.95 (1H, t, O−CH−N), 7.38−7.49 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
Vj	295		81 (8.15)	$C_{17}H_{18}N_4O_7Se$	470	2.21 (6H, s, 2 CH_3CO), 2.65 (2H, dd, C−CH_2−C), 4.31 (1H, m, CH−O), 4.34 (2H, d, $-CH_2-O$), 5.42 (1H, m, −CH−O), 5.95 (1H, t, O−CH−N), 7.70−8.26 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
VIa	233		85 (1.00)	$C_{19}H_{21}N_3O_9Se$	515	2.21 (9H, s, 3 CH_3CO), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.44−7.46 (5H, m, ArH), 8.77 (1H, s, N=CH−N)
VIb	274		82 (1.30)	$C_{20}H_{23}N_3O_{10}Se$	545	2.21 (9H, s, 3 CH_3CO), 3.83 (3H, s, CH_3O), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 6.99−7.33 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
VIc	275		89 (1.45)	$C_{20}H_{23}N_3O_9Se$	529	2.21 (9H, s, 3 CH_3CO), 2.34 (3H, s, CH_3), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.00−7.33 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
VId	258		81 (1.00)	$C_{19}H_{20}ClN_3O_9Se$	549	2.21 (9H, s, 3 CH_3CO), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.38−7.49 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
VIe	245		80 (1.15)	$C_{19}H_{20}N_4O_{11}Se$	560	2.21 (9H, s, 3 CH_3CO), 4.34 (2H, d, $-CH_2-O$), 4.90 (2H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.70−8.26 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
VIf	267		87 (1.30)	$C_{17}H_{19}N_3O_7Se$	457	2.21 (6H, s, 2 CH_3CO), 2.65 (2H, dd, C−CH_2−C), 4.34 (2H, d, $-CH_2-O$), 4.90 (1H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.24−7.55 (5H, m, ArH), 8.77 (1H, s, N=CH−N)
VIg	276		87 (1.30)	$C_{18}H_{21}N_3O_8Se$	487	2.21 (6H, s, 2 CH_3CO), 3.83 (3H, s, CH_3O), 2.65 (2H, dd, C−CH_2−C), 4.34 (2H, d, $-CH_2-O$), 4.90 (1H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 6.99−7.33 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
VIh	287		88 (1.45)	$C_{18}H_{21}N_3O_7Se$	471	2.21 (6H, s, 2 CH_3CO), 2.34 (3H, s, CH_3), 2.65 (2H, dd, C−CH_2−C), 4.34 (2H, d, $-CH_2-O$), 4.90 (1H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.38−7.49 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
VIi	265		82 (2.00)	$C_{17}H_{18}ClN_3O_7Se$	491	2.21 (6H, s, 2 CH_3CO), 2.65 (2H, dd, C−CH_2−C), 4.34 (2H, d, $-CH_2-O$), 4.90 (1H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.38−7.49 (4H, m, ArH), 8.77 (1H, s, N=CH−N)
VIj	276		82 (2.00)	$C_{17}H_{18}N_4O_9Se$	502	2.21 (6H, s, 2 CH_3CO), 2.65 (2H, dd, C−CH_2−C), 4.34 (2H, d, $-CH_2-O$), 4.90 (1H, dd, 2 CH−O), 5.42 (1H, m, −CH−O), 6.54 (1H, d, O−CH−N), 7.70−8.26 (4H, m, ArH), 8.77 (1H, s, N=CH−N)

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Table 1. continued

compd	mp, °C	yield,[a] % (s)	yield,[b] % (h)	mol formula[c]	M^+, m/z	^{1}H NMR (δ ppm) ($CDCl_3$)
VIIa	273		85 (2.00)	$C_{13}H_{15}N_3O_6Se$	389	3.65 (3H, s, 3 −OH), 3.79 (2H, d,−CH_2−O), 4.40 (1H, m, −CH−O), 4.51 (1H, dd, −CH−O), 4.75 (1H, dd, −CH−O), 6.03 (1H, d, N−CH−O), 7.44−7.55 (5H, m, ArH), 8.77 (1H, s, N═CH−N)
VIIb	282		87 (1.30)	$C_{14}H_{17}N_3O_7Se$	419	3.65 (3H, s, 3 −OH), 3.79 (2H, d,−CH_2−O), 3.83 (3H, s, CH_3O), 4.40 (1H, m, −CH−O), 4.51 (1H, dd, −CH−O), 4.75 (1H, dd, −CH−O), 6.03 (1H, d, N−CH−O), 7.44−7.55 (4H, m, ArH), 8.77 (1H, s, N═CH−N)
VIIc	271		88 (1.45)	$C_{14}H_{17}N_3O_6Se$	403	2.34 (3H, s, CH_3), 3.65 (3H, s, 3 −OH), 3.79 (2H, d,−CH_2−O), 4.40 (1H, m, −CH−O), 4.51 (1H, dd, −CH−O), 4.75 (1H, dd, −CH−O), 6.03 (1H, d, N−CH−O), 6.99−7.33 (4H, m, ArH), 8.77 (1H, s, N═CH−N)
VIId	267		84 (2.00)	$C_{13}H_{14}ClN_3O_6Se$	423	3.65 (3H, s, 3 −OH), 3.79 (2H, d,−CH_2−O), 4.40 (1H, m, −CH−O), 4.51 (1H, dd, −CH−O), 4.75 (1H, dd, −CH−O), 6.03 (1H, d, N−CH−O), 7.38−7.49 (4H, m, ArH), 8.77 (1H, s, N═CH−N)
VIIe	256		82 (2.00)	$C_{13}H_{14}N_4O_8Se$	444	3.65 (3H, s, 3 −OH), 3.79 (2H, d,−CH_2−O), 4.40 (1H, m, −CH−O), 4.51 (1H, dd, −CH−O), 4.75 (1H, dd, −CH−O), 6.03 (1H, d, N−CH−O), 7.70−8.26 (4H, m, ArH), 8.77 (1H, s, N═CH−N)
VIIf	271		86 (2.00)	$C_{13}H_{15}N_3O_5Se$	373	2.56 (2H, dd, C−CH_2−C), 3.57 (1H, dd, −CH−O), 3.65 (2H, s, 2 −OH), 3.79 (2H, d, −CH_2−O), 4.40 (1H, m, −CH−O), 5.95 (1H, t, N−CH−O), 7.44−7.55 (5H, m, ArH), 8.77 (1H, s, N═CH−N)
VIIg	283		87 (2.30)	$C_{14}H_{17}N_3O_6Se$	403	2.56 (2H, dd, C−CH_2−C), 3.57 (1H, dd, −CH−O), 3.65 (2H, s, 2 −OH), 3.79 (2H, d, −CH_2−O), 3.83 (3H, s, CH_3O), 4.40 (1H, m, −CH−O), 5.95 (1H, t, N−CH−O), 7.38−7.49 (4H, m, ArH), 8.77 (1H, s, N═CH−N)
VIIh	288		89 (2.30)	$C_{14}H_{17}N_3O_5Se$	387	2.56 (2H, dd, C−CH_2−C), 2.34 (3H, s, CH_3), 3.57 (1H, dd, −CH−O), 3.65 (2H, s, 2 −OH), 3.79 (2H, d, −CH_2−O), 4.40 (1H, m, −CH−O), 5.95 (1H, t, N−CH−O), 7.38−7.49 (4H, m, ArH), 8.77 (1H, s, N═CH−N)
VIIi	288		85 (2.00)	$C_{13}H_{14}ClN_3O_5Se$	407	2.56 (2H, dd, C−CH_2−C), 3.57 (1H, dd, −CH−O), 3.65 (2H, s, 2 −OH), 3.79 (2H, d, −CH_2−O), 4.40 (1H, m, −CH−O), 5.95 (1H, t, N−CH−O), 7.38−7.49 (4H, m, ArH), 8.77 (1H, s, N═CH−N)
VIIj	266		81 (2.00)	$C_{13}H_{14}N_4O_7Se$	418	2.56 (2H, dd, C−CH_2−C), 3.57 (1H, dd, −CH−O), 3.65 (2H, s, 2 −OH), 3.79 (2H, d, −CH_2−O), 4.40 (1H, m, −CH−O), 5.95 (1H, t, N−CH−O), 7.70−8.26 (4H, m, ArH), 8.77 (1H, s, N═CH−N)

[a]Isolated yield with montmorillonite K 10 clay under microwave irradiation. [b]Overall yield for the corresponding thermal process. [c]Satisfactory elemental microanalysis obtained, C ± 0.07, H ± 0.09, N ± 0.06.

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Table 2. Antifungal Screening Results of Compounds VIa−j and VIIa−j

	av % inhibition after 96 h against					
	F. oxysporum			*P. citrinum*		
compd	1000 μg/mL	100 μg/mL	10 μg/mL	1000 μg/mL	100 μg/mL	10 μg/mL
VIa	41	32	15	38	30	12
VIb	53	44	16	47	32	17
VIc	52	37	17	51	42	21
VId	55	29	14	53	39	22
VIe	65	55	30	62	41	24
VIf	45	33	25	42	32	23
VIg	65	25	17	64	35	24
VIh	45	35	26	42	31	17
VIi	54	26	15	51	35	16
VIj	54	28	16	51	34	18
VIIa	82	65	50	89	42	35
VIIb	100	68	55	99	49	39
VIIc	88	80	62	80	78	69
VIId	100	72	44	97	65	36
VIIe	81	48	35	86	59	37
VIIf	77	42	33	81	74	65
VIIg	91	76	65	76	48	42
VIIh	81	75	61	80	74	67
VIIi	81	56	32	75	65	31
VIIj	82	60	41	87	63	33
griseofulvin	100	95	91	100	94	90
Dithane M-45	100	91	86	100	95	89

sodium nitrite in 15 mL of water was added dropwise to the mixture over a period of 15 min. The mixture was stirred for another 30 min at 0 °C to obtain a nearly colorless solution, substituted/unsubstituted aryldiazonium chloride (**IVa−e**). Compound **IVa−e** was added dropwise to a mixture potassium 1-acetylated ribosyl/deoxyribosyl-1*H*-1,2,4-triazole-3-selenolate (**IIIa,b**) during 1 h, and 8.41 g (0.15 mol) of KOH in 20 mL of water was added carefully at the same time to keep the pH at ∼12. After 5 h of stirring at 0 °C, methanol was distilled off under vacuum, and the mixture was filtered. The filtrate was extracted with chloroform (3 × 25 mL), dried over anhydrous sodium sulfate, and purified with flash chromatography through silica gel with hexane:EtOAc (1:1 v/v) to give pure **Va−j**.

3-(Substituted/unsubstituted phenylselenonyl)-1-acetylated ribosyl/acetylated deoxyribosyl-1*H*-1,2,4-triazole (VIa−j). Following the standard procedure,[23] a solution of NaOH (0.68 g, 0.017 mol) and $Na_2HPO_4·H_2O$ (0.9 g, 0.0025 mol) in 10 mL of water was added carefully to a vigorously stirred solution of the corresponding 3-(substituted/unsubstituted phenylselenonyl)-1-acetylribosyl/deoxyribosyl-1*H*-1,2,4-triazole (0.0025 mol) (**Va−j**) in 30 mL of methanol, followed by the quick addition of 10 mL of aqueous of Oxone (3.07 g, 0.005 mol). After room temperature had been maintained during 20 min of stirring, the mixture was filtered and washed with 30 mL of methanol. The filtrate was evaporated under reduced pressure to remove the methanol, neutralized with 6 M NaOH, filtered, and dried in vacuum desiccators to give **VIa−j**.

3-(Substituted/unsubstituted phenylselenonyl)-1-ribosyl/deoxyribosyl-1*H*-1,2,4-triazole (VIIa−j). A mixture of (**VIa−j**) (2.5 mmol) and MeONa (2.5 mmol) was dissolved in dry MeOH (20 mL) and stirred for about 2 h at rt. The completion of the reaction was monitored by TLC using hexane:MeOH (6:4 v/v). The reaction mixture was cooled to rt. This was neutralized with dilute HCl. The product thus obtained was filtered and recrystallized from ethanol to obtain analytically pure **VIIa−j**.

Antifungal Screening. The in vitro antifungal screening of the compounds **VIa−j** and **VIIa−j** was carried out against *Fusarium oxysporum* and *Penicillium citrinum* by poisoned food technique[24] at 10, 100, and 1000 μg/mL concentration using commercial fungicide, griseofulvin and Dithane M-45, as standards and Czapek's agar as medium as previously described.[25−27] There were three replicate assays in each, and six replicate controls were used. No remarkable morphological change was observed in the developing fungi. The test fungi were inoculated in the center of the Petri dishes and incubated at 28 ± 1 °C for 96 h. After this time, the percent inhibition of the mycelial growth compared with that in control dishes was recorded.

$$\%\ \text{inhibition} = 100[(\text{av hyphal diameter in the control}) - (\text{av hyphal diameter in the test})]/(\text{av hyphal diameter in the control})$$

Most of the screened compounds showed promising fungicidal activity at 1000 μg/mL concentration with both the test fungi *Fusarium oxysporum* and *Penicillium citrinum* (Table 2). Among the tested compounds, **VIIb** and **VIId** displayed fungicidal action comparable with that of griseofulvin and Dithane M-45 at 1000 μg/mL concentration and inhibited 42−67% mycelial growth of both fungal species even at the lowest concentration. This demonstrates that the presence of selenonyl-1-ribosyl with the 1,2,4-triazole nucleus resulted in appreciable enhancement of fungitoxicity of these compounds.

For the most active compounds **VIIb** and **VIId** it was ascertained whether they are fungistatic or fungicidal. Thus, following the procedure of Garber and Houston,[28] it was found that compounds **VIIb** and **VIId** caused complete inhibition of mycelial growth of the test fungi in treated as well as reinoculated dishes and hence were fungicidal.

The present study indicates that the 1,2,4-triazole framework incorporated with the selenonyl-1-ribosyl nucleus reported herein might be useful for developing efficacious fungicides by a suitable combination of heterocyclic moiety and substituent present on the aromatic ring.

RESULTS AND DISCUSSION

Most of the screened compounds have significant fungitoxicity at 1000 μg/mL (Table 2) against both tested fungi, but their toxicity considerably decreased on dilution (100 and 10 μg/mL). Of the tested compounds, the most active, **VIIb** and **VIId**, displayed fungicidal action comparable with that of griseofulvin and Dithane M-45 at 1000 μg/mL and inhibited 12−69% mycelial growth of both fungal species even at the lowest concentration. Compounds **VIa−j**, which have acetylated hydroxyl groups, are less fungitoxic than **VIIa−j**. This demonstrates that the presence of ribose sugar with the 1,2,4-triazole nucleus resulted in appreciable enhancement of fungitoxicity of these compounds. The present study indicates that the 1,2,4-triazole framework with ribose sugar reported herein might be useful for developing efficacious fungicides by suitable structural variation in the aryl nucleus.

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Notes

The authors declare no competing financial interest.

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