

Note

Synthesis and fungicidal activity of some 3-(5-aryl-1,3,4-thiadiazol-2-yl)-1-(β -D-glucopyranosyl)-5-alkyl-2-thio-4-imidazolidinones

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3-(5-Aryl-1,3,4-thiadiazol-2-yl)-1-(β -D-glucopyranosyl)-5-alkyl-2-thio-4-imidazolidinones **5** have been conveniently prepared from 3-(5-aryl-1,3,4-thiadiazol-2-yl)-5-alkyl-2-thio-4-imidazolidinones **3** by reaction of β -D-1,2,3,4,6-penta-O-acetylglucopyranose and iodine. Compounds **3** are synthesized by reported method from *N*-(5-aryl-1,3,4-thiadiazol-2-yl) thioureas **2** and α -chloroalkanoic acid in dry pyridine. All the compounds have been tested *in vitro* for their antifungal activity against the two fungal species *Cephalosporium sacchari*, *Colletotrichum falcate* and *Helminthosporium oryzae*.

Keywords: Thiadiazole, imidazolidinone, glucopyranosyl, *Cephalosporium sacchari*, *Colletotrichum falcate*, *Helminthosporium oryzae*

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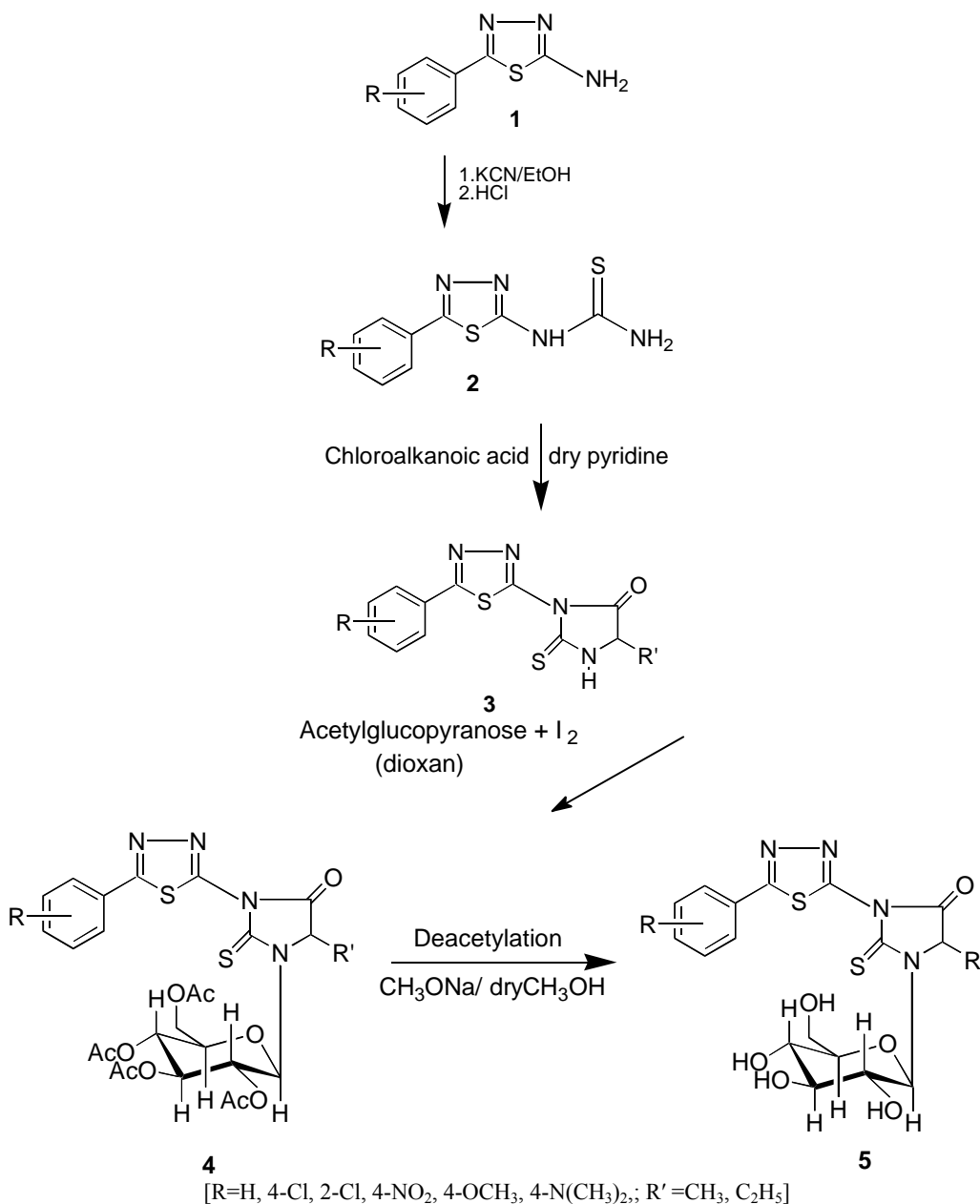
Thiohydantoin belongs to a class of compounds, which got attention in recent years on account of their use as potent fungicides, having low rate application. 1,3,4-thiadiazole nuclei are well known for their varied application in the area of pesticides¹⁻⁵. Literature survey revealed that compounds having hydantoin skeleton in their structure exhibited both bactericidal⁶ and herbicidal activity, e.g. phosphoryl amino phenyl hydantoin⁷, hydantocidin⁸⁻¹⁰. The most important hydantoin fungicide¹¹ is iprodione i.e. [(3,5-dichlorophenyl)-N-isopropylhydantoin-1-carboximide]. Similarly, there are many thiohydantoin compounds which exhibit fungicidal activity¹². Antibiotics polyoxins¹³ and nikkomycins¹⁴ are peptidyl nucleosides containing carbohydrate moiety. These antibiotics are reported to exhibit marked activity against phytopathogenic fungi by inhibiting the

activity of chitin synthetase and thus biosynthesis of chitin. On the basis of these observation it was envisaged to couple the biolabile thiadiazolyl thiohydantoin and glucopyranose rings¹⁵⁻¹⁷ in anticipation that this combination will greatly enhance the fungicidal activity. The investigation further appeared interesting because no such report on thiohydantoin having thiadiazole ring in their structure is available in literature so far.

The desired compounds **5a-l** have been synthesized in 58-80% yield, by refluxing compound **3**, β -D-1,2,3,4,6-penta-O-acetylglucopyranose and iodine to give the compound **4**, which on deacetylation furnished the compound **5** (**Scheme I**). The starting materials 3-(5-aryl-1,3,4-thiadiazol-2-yl)-5-alkyl-2-thio-4-imidazolidinones **3a-l** were synthesized according to the method of Giri and Khare¹². The characterisation data of different title compounds **5** synthesized are recorded in **Table I**.

Fungicidal screening

The fungicidal activity was evaluated against *Cephalosporium saccharii*, *Colletotrichum falcatum* and *Helminthosporium oryzae* by the usual agar-plate technique¹⁸ in Czapek's agar medium at 1000 ppm, 100 ppm and 10 ppm concentrations using Mancozeb M-45, a commercial fungicide, as standard. The compounds were tested either as solution or suspension in acetone-water (20:80 v/v) mixture. The standard solution or suspensions of different concentration of each compound viz. 10000 ppm, 1000 ppm and 100 ppm were prepared in acetone-water (20:80 v/v) mixture. 1 mL of each concentration of the tested compound was added separately to presterilized petri dishes containing 9 mL of sterilized Czapek's agar medium to maintain the final concentrations of 1000 ppm, 100 ppm and 10 ppm. The compound was thoroughly mixed with the medium by rotating the plates on table top, thus swirling the contents. A fungal disk of 5 mm diameter cut out with the help of sterilized cork borer from the periphery of one week old culture of test fungus already planted on the Czapek's agar medium, was inoculated in the centre of each petri-dish containing 9 mL of Czapek's agar medium. The number of replications in each case were three. After 96 hr the



Scheme I

diameter of fungal growth zone was measured. The results were expressed in terms of the percentage growth inhibition, by comparing with growth on control plate. Thus:

$$\text{Percentage inhibition} = \frac{(C-T) \times 100}{C}$$

where, C = Diameter (in mm) of the fungal colony in control plate.

T = Diameter (in mm) of the fungal colony in treated plate.

The antifungal data of compounds are listed in **Table II**.

Results and Discussion

The antifungal activity data on *Cephalosporium saccharii*, *Colletotrichum falcatum* and *Helminthosporium oryzae* showed that compounds **5b**, **5c**, **5d**, **5h**, **5i** and **5k** are fairly active on all the three fungal species. They inhibited the fungus growth up to 82-98% at 1000 ppm and 52-71% at 100 ppm concentration. So, further screening of these compounds on wider range of fungi as well as at higher dilution is in progress. It is to be noted that presence of more electronegative toxophores (-Cl, -OCH₃, -NO₂) in this series of compounds

Table I—Characterization data of compounds **5a-l**

Compd	R	Yield (%)	m.p. °C	R _f [*]	Mol. formula R'=CH ₃	% Found (Calcd)			Spectral data ¹ H NMR δ (ppm)	MS M ⁺ (m/z)
						C	H	N		
5a	H	70	300	0.63	C ₁₈ H ₂₀ O ₆ N ₄ S ₂	47.66 (47.78)	4.51 4.42	12.40 12.38)	2.03 (m, 2H, CH ₂); 2.24 (s, 3H, CH ₃); 4.02-4.35 (m, 3H, 2'H, 3'H, 4'H); 5.06-5.50 (m, 5H, 5'H, 4×OH); 6.32 (s, 1H, NCH); 7.20-7.61 (m, 5H, ArH)	452
5b	4-Cl	72	298-99	0.79	C ₁₈ H ₁₉ O ₆ N ₄ S ₂ Cl	44.41 (44.39)	3.87 3.90	11.49 11.51)	2.04 (m, 2H, CH ₂); 2.24 (s, 3H, CH ₃); 4.05-4.38 (m, 3H, 2'H, 3'H, 4'H); 5.15-5.59 (m, 5H, 5'H, 4×OH); 6.36 (s, 1H, NCH); 7.23-7.65 (m, 4H, ArH)	
5c	2-Cl	69	290-93	0.65	C ₁₈ H ₁₉ O ₆ N ₄ S ₂ Cl	44.25 (44.39)	3.99 3.90	11.64 11.51)	2.01 (m, 2H, CH ₂); 2.20 (s, 3H, CH ₃); 4.06-4.40 (m, 3H, 2'H, 3'H, 4'H); 5.20-5.63 (m, 5H, 5'H, 4×OH); 6.38 (s, 1H, NCH); 7.22-7.66 (m, 4H, ArH)	
5d	4-NO ₂	60	288	0.73	C ₁₈ H ₁₉ O ₈ N ₅ S ₂	43.53 (43.46)	3.73 3.82	14.17 14.08)	2.01(m, 2H, CH ₂); 2.20 (s, 3H, CH ₃); 4.06-4.41 (m, 3H, 2'H, 3'H, 4'H); 5.06-5.43 (m, 5H, 5'H, 4×OH); 6.42(s, 1H, NCH); 7.24-7.68 (m, 4H, ArH)	497
5e	4-OCH ₃	59	267	0.69	C ₁₉ H ₂₂ O ₇ N ₄ S ₂	47.26 (47.30)	4.62 4.56	11.78 11.61)	2.03 (m, 2H, CH ₂); 2.22 (s, 3H, CH ₃); 3.89 (s, 3H, OCH ₃); 4.05-4.39 (m, 3H, 2'H, 3'H, 4'H); 5.21-5.63 (m, 5H, 5'H, 4×OH); 6.52 (s, 1H, NCH); 7.23-7.66 (m, 4H, ArH)	
5f	4-N(CH ₃) ₂	63	276-78	0.63	C ₂₀ H ₂₅ O ₆ N ₅ S ₂	48.52 (48.48)	5.19 5.05	14.03 14.14)	2.03 (m, 2H, CH ₂); 2.24 (s, 3H, CH ₃); 3.02 (s, 6H, Me ₂ N); 4.06-4.39 (m, 3H, 2'H, 3'H, 4'H); 5.18-5.61(m, 5H, 5'H, 4×OH); 6.33 (s, 1H, NCH); 7.25-7.68 (m, 4H, ArH)	
5g	H	80	295	0.68	R'=C ₂ H ₅ C ₁₉ H ₂₂ O ₆ N ₄ S ₂	48.90 (48.92)	4.69 4.72	12.12 12.01)	2.04 (m, 4H, 2×CH ₂); 1.31(t, 3H, CH ₃); 4.05-4.39 (m, 3H, 2'H, 3'H, 4'H); 5.06-5.52 (m, 5H, 5'H, 4×OH); 6.48 (s, 1H, NCH); 7.21-7.61 (m, 5H, ArH)	
5h	4-Cl	73	288	0.76	C ₁₉ H ₂₁ O ₆ N ₄ S ₂ Cl	45.38 (45.55)	4.30 4.19	11.16 11.18)	2.03 (m, 4H, 2×CH ₂); 1.31(t, 3H, CH ₃); 4.02-4.33 (m, 3H, 2'H, 3'H, 4'H); 5.23-5.61(m, 5H, 5'H, 4×OH); 6.32 (s, 1H, NCH); 7.25-7.66 (m, 4H, ArH)	
5i	2-Cl	68	272	0.63	C ₁₉ H ₂₁ O ₆ N ₄ S ₂ Cl	45.38 (45.55)	4.21 4.19	11.21 11.18)	2.04 (m, 4H, 2×CH ₂); 1.31(t, 3H, CH ₃); 4.03-4.37 (m, 3H, 2'H, 3'H, 4'H); 5.23-5.61(m, 5H, 5'H, 4×OH); 6.42 (s, 1H, NCH); 7.24-7.66 (m, 4H, ArH)	

—Contd

Table I—Characterization data of compounds **5a-l**—*Contd*

Compd	R	Yield (%)	m.p. °C	R _f *	Mol. formula R'=CH ₃	% Found (Calcd)			Spectral data	
						C	H	N	¹ H NMR δ (ppm)	MS M ⁺ (m/z)
5j	4-NO ₂	72	289-91	0.71	C ₁₉ H ₂₁ O ₈ N ₅ S ₂	44.62 (44.61)	4.18 4.10	13.58 13.69)	2.03 (m, 4H, 2×CH ₂); 1.28 (t, 3H, CH ₃); 4.05-4.40 (m, 3H, 2'H, 3'H, 4'H); 5.06-5.43 (m, 5H, 5'H, 4×OH); 6.32 (s, 1H, NCH); 7.23-7.68 (m, 4H, ArH)	511
5k	4-OCH ₃	70	265	0.65	C ₂₀ H ₂₄ O ₇ N ₄ S ₂	48.32 (48.38)	4.82 4.83	11.36 11.29)	2.04 (m, 4H, 2×CH ₂); 1.29 (t, 3H, CH ₃); 3.88 (s, 1H, OCH ₃); 4.05-4.41 (m, 3H, 2'H, 3'H, 4'H); 5.10-5.51(m, 5H, 5'H, 4×OH); 6.38 (s, 1H, NCH); 7.26-7.69 (m, 4H, ArH)	496
5l	4-N(CH ₃) ₂	58	283-85	0.61	C ₂₁ H ₂₇ O ₆ N ₅ S ₂	49.51 (49.50)	5.36 5.30	13.63 13.75)	2.04 (m, 4H, 2×CH ₂); 1.31(t, 3H, CH ₃); 3.02 (s, 6H, Me ₂ N); 4.03-4.39 (m, 3H, 2'H, 3'H, 4'H); 5.06-5.32 (m, 5H, 5'H, 4×OH); 6.31(s, 1H, NCH); 7.26-7.66 (m, 4H, ArH)	

* Solvent system: Ethyl acetate-pet. ether (1 : 5)

Table II—Fungicidal activity of compounds **5a-l**

Compd 5	Average% inhibition against								
	<i>Cephalosporium saccharii</i>			<i>Colletotrichum falcatum</i>			<i>Helminthosporium oryzae</i>		
	1000ppm	100ppm	10ppm	1000ppm	100ppm	10ppm	1000ppm	100ppm	10ppm
a	75	68	47	77	50	46	82	63	54
b	98	63	42	86	67	39	96	69	48
c	96	69	30	87	63	41	93	71	50
d	87	61	46	78	65	37	83	61	42
e	88	59	48	79	53	40	88	56	50
f	84	67	41	80	55	39	83	51	43
g	79	51	36	76	53	33	78	52	40
h	93	58	37	82	52	34	91	64	43
i	91	64	35	85	58	36	88	66	45
j	82	56	41	79	60	32	78	56	37
k	89	54	45	83	58	41	86	58	47
l	81	57	42	80	51	37	75	52	32
Mancozeb M-45*	100	82	63	89	70	56	100	86	58

*A commercial fungicide

enhanced the antifungal activity. These data are in accordance with the fact that the combinations of some modified bioactive nitrogen heterocycles like thia-diazolyl thiohydantoin with glucose moiety have resulted in more potent nucleosides. Presumably, these nucleosides interfere in the synthesis of nucleic acid and

cell wall of fungi and thus inhibit different metabolic activity of fungi and arrest the fungal cell growth.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra in KBr were recorded

on a Perkin-Elmer 881 infrared spectrometer (ν_{\max} cm^{-1}); Mass spectra were obtained on a Hewlett Packard mass spectrometer operating at 70 eV and ^1H NMR spectra in CDCl_3 on a Bruker Avance DPX 200 MHz spectrometer using TMS as internal reference (chemical shifts in δ , ppm). ^1H NMR spectra of the final compound **5** were found almost identical to that of the constituents compound **3** and the β -glucopyranose, with only difference of absence of –NH peak of compound **3**.

All the starting materials were synthesized by the method given in literature and identified from their ^1H NMR and IR spectra and micro analysis of these compounds were in satisfactory agreement with the anticipated structures. All the tested compounds were purified by column chromatography using silica gel and ethyl acetate-petroleum ether (1:5) as eluant. The compounds purified were also homogenous on thin layer chromatography (TLC).

2-Amino-5-aryl-1,3,4-thiadiazoles 1. These compounds were prepared by the method of Maffii *et al.*¹⁹.

N-(5-aryl-1,3,4-thiadiazol-2-yl)thioureas 2. These compounds were prepared according to the method of Vishwanathan *et al.*²⁰

3-(5-aryl-1,3,4-thiadiazol-2-yl)-5-alkyl-2-thio-4-imidazolidinones 3. These compounds were prepared according to the method of Giri and Khare¹².

General procedure for the preparation of 3-(5-aryl-1,3,4-thiadiazol-2-yl)-1-(β -D-2,3,4,6-tetra-O-acetylglucopyranosyl)-5-alkyl-2-thio-4-imidazolidinones 4. A mixture of 3-(5-aryl-1,3,4-thiadiazol-2-yl)-5-alkyl-2-thio-4-imidazolidinones (0.002 mole), β -penta-O-acetylglucopyranose (0.002 mole) and iodine (0.0026 mole) were dissolved in a minimum amount of dioxan. The reaction mixture was refluxed for 4-5 hr. After cooling, the mixture was poured into aqueous solution of sodium thiosulphate to remove excess of iodine. The desired product thus obtained was filtered, washed with water and purified by recrystallization from ethanol.

3-(5-aryl-1,3,4-thiadiazol-2-yl)-1-(β -D-glucopyranosyl)-5-alkyl-2-thio-4-imidazolidinones 5. The compound **4** (0.0016 mole) in 20 mL dry MeOH and 1 mL solution of sodium methoxide (prepared by adding 0.1 g of Na in 20 mL of dry MeOH) were taken in a stoppered flask. The mixture was allowed

to stand for 2-3 hr with occasional shaking. The solution was neutralised with dil. HCl. Deacetylation took place. The product thus precipitated was filtered, washed and purified by recrystallization from ethanol. The characterization data of compound **5** are recorded in **Table I**.

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