Synthesis of Some 2-Aryloxy methyl -4-(β-D-glucopyranosyl)-1,3,4-oxadiazolin-5-thiones Derivatives and their Antifungal Activities

Balmukund Tiwari, Shiv Shankar Sharma, Atul Kumar Srivastava*

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Abstract

The 1,3,4-oxadiazoles are observed as a significant class of heterocyclic substances having enormous range of biological actions, including fungicidal, herbicidal, *etc*. so they attracted the organic chemist very much. Since, the glycosides have a variety of pharmacological effects so in present study, we aimed to introduce a 1,3,4-oxadiazole group into glucopyranosyl moiety to design a series of novel glucopyranosyl derivatives of 1,3,4-oxadiazolone, as some oxadiazolone derivatives have been reported to exhibit antifungal activity.

In current study the some 2-aryloxy methyl-4-(β-D-glucopyranosyl-1,3,4-oxadiazolin-5-thiones (**4a-g**) have been conveniently prepared from the deacetylation of 2-aryloxy methyl-4-(β-D-2,3,4,6-tetra-*O*-acetylglucopyronosyl)-1,3,4-oxadiazolin-5-thiones (**3a-g**). The compounds (**3a-g**) were obtained from the reaction of 2-aryloxy methyl-1,3,4-oxadiazolin-5-thiones (**2a-g**) with 2,3,4,6-tetra-*O*-acetylglucopyranose and I_2 in dioxane. The novel synthesized compounds have been tested *in vitro* testing for their antifungal activity against the all four fungal species. The results of antifungal activities showed that some of the target compounds exhibited good antifungal activities.

Keywords: Antifungal activities, Tetra-*O*-acetylglucopyranose, Oxadiazoles, Thiones

P.G. Department of Chemistry, Magadh University, Bodh Gaya-824234, India

*Corresponding author: E-mail: drakschem@gmail.com

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Introduction

The fungi are responsible for the great loss to our food supplies both in fields and stores. In addition to variety of plant and animal diseases, the fungi cause deterioration and destruction of foodstuffs, fabrics leather *etc*. during storage.

In the recent past there is a huge growth in the field of bioactive heterocycles due to their pharmacological and pesticidal importance [1-5]. The oxadiazoles are heterocyclic compounds which shows wide range of physiologically activity, including fungicidal and herbicidal effects. It has been observed that the 1,3,4-oxadiazole [6-11] derivatives have bactericidal, antifungal and herbicidal biological effects.

According to earlier research, glycoside [12-20] have a variety of pharmacological effects, including antiviral, antibacterial, anticancer, antioxidant and anti-HIV effects.

Additionally, studies revealed that glycoside derivatives have extremely strong inhibitory effects on plant pathogens. Ningnanmycin, as an example [21].

Furthermore, it was shown that glycosylation is one of the efficient methods for enhancing the functional activity of active lead compounds and develop novel drugs [22].

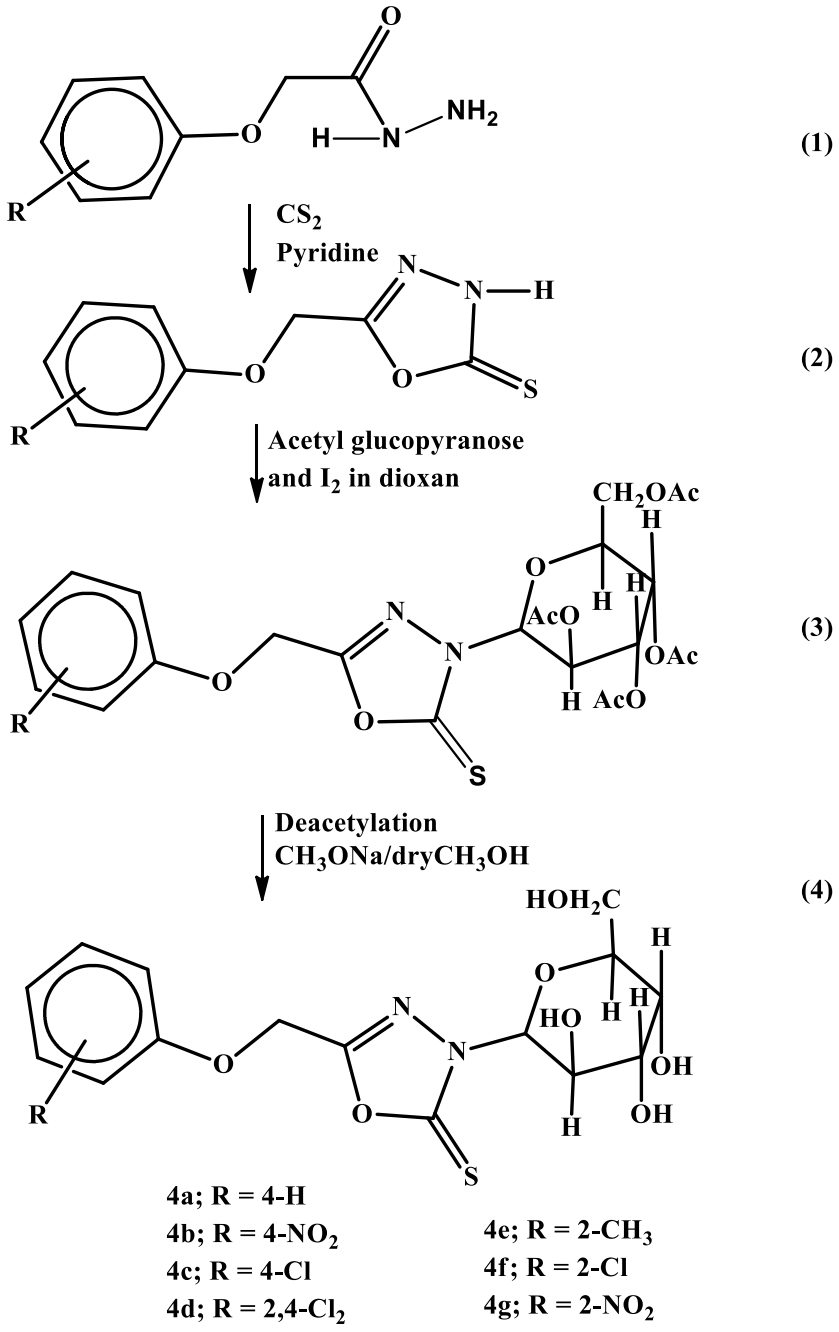
In light of above background it was anticipiated to design a series of novel 2-aryloxymethyl-4-(β-D-glucopyranosyl-1,3,4-oxadiazolin-5-thiones (**4a-g**) by combining the 2-aryloxy methyl-1,3,4-oxadiazolin-5-thiones with the D-glucopyranosyl moiety [23] and then evaluate for their antifungal activities as some oxadiazolone derivatives have been reported to exhibit antifungal activity [24].

These compounds have been screened for their antifungal activity against four fungal species *i.e. C. falactum, F. oxysporum, C. saccharii* and *A. niger*. Among fungal diseases Red rot of sugarcane caused by *C. falactum* and wilt disease of sugarcane caused by *C. saccharii*. It is very widespread in north Bihar and Uttar Pradesh where sugarcane is grown in large quantities. The *F. oxysporum* is a saprophytic fungus, it is a causal agent of the wilt disease of pigeon pea, very destructive in parts of Uttar Pradesh and Bihar in rainy season. On the other hand the *A. niger*, popularly known as ' black mould, is a saprophytic fungus. It is a causal agent of several plant diseases like collar rot of onion, crown rot of peanut *etc*.

According to the findings from antifungal Screening data, some of the target compounds have potent antifungal properties. Especially, the compounds **4d** showed higher bioactivities against the fungal species.

RESULTS AND DISCUSSION

In current study, some 2-aryloxymethyl-(4-β-D-2,3,4,6-tetra-O-acetyl glucopyranosyl)-1,3,4-oxadiazolin-5-thiones (**3a-g**) were deacetylated using sodium ethoxide in dry methyl alcohol to produce 2-aryloxymethyl-4-(β-D-glucopyranosyl-1,3,4-oxadiazolin-5-thiones (**4a-g**) (**Scheme-I**) with a yield of 52-64% . The required **3a-g**, in turn, were synthesized by the reaction of 2-aryloxy methyl-1,3,4-oxadiazolin-5-thiones (**2a-g**), with acetyl glucopyranose and I_2 were refluxed in dioxane to synthesized the compound **3**.



Scheme-I: Synthesis of some 2-aryloxymethyl-4-(β-D-glucopyranosyl)-1,3,4-oxadiazolin-5-thione

All the synthesized compounds were characterized by the physicochemical properties (Table-1) and spectral characteristic .The chemical structures of the synthesized some2-Aryloxymethyl-4-(β -D-glucopyranosyl)-1,3,4-oxadiazolin-5-thiones **(4a-g)** were established by ^{1}H NMR, IR and elemental analysis.

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF (**4a-g**)

Compound	R	Yield (%)	m.p. (°C)	Elemental analysis (%): Experimental (calcd.)		
				C	H	N
4a	4-H	52	172	46.93 (48.64)	4.31 (4.90)	7.21 (7.56)
4b	4-NO_2	63	242	42.93 (43.37)	3.65 (4.13)	9.81 (10.12)
4c	4-Cl	64	198	43.95 (44.51)	3.97 (4.23)	5.93 (6.92)
4d	2,4-Cl_2	58	202	39.77 (41.02)	3.13 (3.67)	5.97 (6.38)
4e	2-CH_3	56	164	48.11 (49.99)	4.11 (5.24)	6.27 (7.29)
4f	2-Cl	61	189	41.96 (44.51)	3.76 (4.23)	5.86 (6.92)
4g	2-NO_2	62	236	41.93 (43.37)	3.15 (4.13)	9.41 (10.12)

The IR spectrum showed characteristic IR band at 1060-1080 cm^{-1} indicated the presence of exocyclic C=S group, the characteristic band at 3342-3366 cm^{-1} indicated the presence of OH group in glucopyranosyl ring, the characteristic band at 1564-1589 cm^{-1} indicated the presence of cyclic C=N group. The characteristic band at 1525-1559 cm^{-1} indicated the presence of aromatic -NO_2 group in compounds **4b** and **4g**.

The ^{1}H NMR spectrum showed characteristic peak at 4.21-4.28 ppm indicated the presence of -OCH_2 group of aryloxymethyl group, peak at 6.14 -6.64 ppm indicated the presence of NCH group. Peak at 7.18-7.32 indicated the presence of aromatic ring. In compound **4e** the ^{1}H NMR peak at 2.21 ppm indicated the presence of CH_3 group attached to aromatic ring.

The spectral characteristic of all the synthesized some 2-aryloxymethyl-4-(β-D-glucopyranosyl)-1,3,4-oxadiazolin-5-thiones (**4a-g**) are given as:

4a: PMR ($CDCl_3$) (ppm): 2.13-2.16 (m, 2H, -CH_2); 4.25-4.39 (m, 3H, 2'H, 3H', 4H'); 5.06-5.55 (m, 5H, 5'H, 4×OH); 6.64 (s, 1H, NCH); 7.26 (m, 4H, ArH); 4.21 (s, 2H, OCH_2). IR (KBr) (cm^{-1}): 1169 (-NCO); 1589 (>C=N-); 1065 (C=S), 3358s (-OH).

4b: PMR ($CDCl_3$) (ppm): 2.01-2.08 (m, 2H, -CH_2); 4.16-4.34 (m, 3H, 2'H, 3H', 4H'); 5.19-5.53 (m, 5H, 5'H, 4×OH); 6.5 4 (s, 1H, NCH); 7.28 (m, 4H, ArH); 4.26 (s, 2H, OCH_2). IR (KBr) (cm^{-1}): 1525 (NO_2) 1174 (-NCO); 1589 (>C=N-); 1060 (C=S), 3366 (-OH).

4c: PMR ($CDCl_3$) (ppm): 2.03-2.09 (m, 2H, -CH_2); 4.16-4.34 (m, 3H, 2'H, 3H', 4H'); 5.09-5.58 (m, 5H, 5'H, 4×OH); 6.5 4 (s, 1H, NCH); 7.28 (m, 4H, ArH); 4.23 (s, 2H, OCH_2). IR (KBr) (cm^{-1}): 1172 (-NCO); 1584 (>C=N-); 1080 (C=S), 3362 (-OH).

4d: PMR ($CDCl_3$) (ppm): 2.01-2.06 (m, 2H, -CH_2); 4.09-4.24 (m, 3H, 2'H, 3H', 4H'); 5.06-5.28 (m, 5H, 5'H, 4×OH); 6.1 4 (s, 1H, NCH); 7.18 (m, 4H, ArH); 4.13 (s, 2H, OCH_2). IR (KBr) (cm^{-1}): 1168 (-NCO); 1564 (>C=N-); 1072 (C=S), 3342 (-OH).

4e: PMR ($CDCl_3$) (ppm): 2.21 (s, 3H, CH_3); 2.06-2.10 (m, 2H, -CH_2); 4.26-4.34 (m, 3H, 2'H, 3H', 4H'); 5.14-5.58 (m, 5H, 5'H, 4×OH); 6.6 4 (s, 1H, NCH); 7.32 (m, 4H, ArH); 4.28 (s, 2H, OCH_2); IR (KBr) (cm^{-1}): 1178 (-NCO); 1574 (>C=N-); 1075 (C=S), 3359 (-OH).

4f: PMR ($CDCl_3$) (ppm): 2.02-2.09 (m, 2H, -CH_2); 4.17-4.35 (m, 3H, 2'H, 3H', 4H'); 5.10-5.68 (m, 5H, 5'H, 4×OH); 6.5 6 (s, 1H, NCH); 7.28 (m, 4H, ArH); 4.21 (s, 2H, OCH_2). IR (KBr) (cm^{-1}): 1171 (-NCO); 1584 (>C=N-); 1063 (C=S), 3364 (-OH).

4g: PMR ($CDCl_3$) (ppm): 2.01-2.09 (m, 2H, -CH_2); 4.15-4.36 (m, 3H, 2'H, 3H', 4H'); 5.19-5.54 (m, 5H, 5'H, 4×OH); 6.5 4 (s, 1H, NCH); 7.26 (m, 4H, ArH); 4.25 (s, 2H, OCH_2). IR (KBr) (cm^{-1}): 1559 (NO_2) 1175 (-NCO); 1589 (>C=N-); 1070 (C=S), 3363 (-OH).

All the seven compounds (**4a-g**) have been tested for antifungal activity. The fungicidal results indicates that all the tested compounds showed strong to moderate activities. It is interesting to mention from fungicidal data all the title compounds (**4a-g**) as stated in Table-2 found to be more active against the four fungal species *Collectotrichum falcatum, Cephalosporium saccharii, Fusarium oxysporum* and *Aspergillus niger* at 1000 ppm but their activity decreased at lower concentration *i.e.* 100 ppm and 10 ppm. The compound **4c** and **4d** showed greater toxicity at 1000 ppm. It is remarkable to mention that –Cl and -NO_2, increased the antifungal activity. In case of 2,4-Cl_2 it was found that they were more effective due to better lipophilic character of Cl group which favours the permeate of the compound through lipoid layer of the fungal cell wall.

TABLE-2
ANTIFUNGAL SCREENING DATA OF 2-ARYLOXY METHYL-4-(β-D-GLUCOPYRANOSYL)-1,3,4-OXADIAZOLIN-5-THIONES

Compd. No.	Average % inhibition against						Average % inhibition against					
	C. falacm			*F. oxysporum*			*C. saccharii*			*A. niger*		
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
4a	81	72	46	84	62	35	78	73	45	83	64	37
4b	91	73	54	91	73	55	93	71	55	86	71	53
4c	92	79	55	93	76	53	89	77	57	84	75	51
4d	95	79	61	93	77	62	94	81	60	81	78	59
4e	83	71	45	84	71	51	83	84	43	88	68	48
4f	85	71	51	85	73	49	87	70	50	85	72	47
4g	89	75	49	87	75	51	86	72	45	86	77	54
Dithane M-45	100	87	63	100	83	64	100	89	65	100	86	60

Experimental

The melting points were established in open capillaries, may be uncorrected. The ^{1}H NMR spectra in $CDCl_3$ were obtained on a Varian EM-360 (200 MHz) spectrometer using TMS as internal reference, while the IR spectra in KBr were obtained as a Perkin-Elmer 881 infrared spectrophotometer (cm^{-1}).

Synthesis of 2-aryloxy methyl-1,3,4-oxadiazolin-5-thiones (2a-g): These were prepared according to the following method.

Typical procedure for 2a: This was prepared by dissolving 2- phenoxymethyl hydrazide in 15mL of pyridine followed by drop wise addition of 15mL of CS_2 . The mixture was refluxed for 6 h and then cooled. The mixture was neutralized with dilHCl, filtered and washed with water. The product crystallized from ethyl alcohol.

2-Aryloxy methyl-4-(β-D-2, 3, 4, 6-tetra-O-acetylglucopyranosyl)-1, 3, 4- oxadiazolins -5-thiones (3a-g)

Typical procedure for 3a: A mixture of 2-phenoxy methyl-1,3,4-oxadiazolin-5-thiaone (**2**) 0.85 g, (1,2,3,4,6-penta-O-acetylglucopyranosyl) 1.85 g and iodine 1.00 g were dissolved in a least amount of dioxane. The reaction mixture was refluxed for 4.5 h. After cooling, the mixture was poured into aqueous solution of sodium thiosulphate (0.38 g) to remove excess of I_2. The product thus precipitated and crystallized from ethyl alcohol.

2-Aryloxy methyl-4-(β-D-glucopyranosyl)-1,3,4-oxadiazolins-5-thiones (4a-g)

Typical procedure for 4a: A mixture of 2-phenoxy methyl-4-(β-D-2,3,4,6-tetra-O-acetyl glucopyronosyl)-1,3,4-oxadiazolin-5-thione (**3**) 0.80 g, 20 mL of dry methanol and 1 mL solution of sodium methoxide were taken in a stopper flask, the mixture was allowed to stand for 2 h with occasional shaking. The solution was neutralized by adding dilute HCl. The product thus precipitated was filtered and crystallized from ethyl alcohol.

The characterization data, m.p., yield are recorded in Table-1.

Antifungal screening: Using standard dithane M-45 (a commercial fungicide), the fungicidal activity were assessed against four fungal species *Collectotrichum falcatum, Cephalosporium saccharii, Fusarium oxysporum* and *Aspergillus niger* by standard agar-plate methods at 1000, 100 and 10 ppm concentrations. There were three replications in each case. The diameter of the fungal growth zone was determined after 96 h. By comparing the results to growth under control, the findings were reported as a percentage growth inhibition.

Thus,

$$\text{Inhibition } (\%) = \frac{C - T}{100}$$

where, C = In control plate, diameter of the fungal colony (mm), T = In treated plate, diameter of the fungal colony (mm).

According to the fungicidal data (Table-2), all of the tested compounds showed strong to moderate activity. It is remarkable to note from antifungal data of all the tested compounds (**4a-g)** exhibited strong antifungal activity against all four fungal species at 1000 ppm, while their activity diminished at lower doses *i.e.* 100 ppm and 10 ppm.

Further, It is also significant to note that the antifungal activities of all the title compounds enhanced in the case of more electronegative oxophores (Cl and NO_2).

These substances disrupt the fungal cell wall, which affects the metabolic processes of the fungi.

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