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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF 2-ARYL-5-(PYRIDIN-4-YL)-1,3,4-OXADIAZOLES DERIVED FROM ISONICOTINIC ACID

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Keywords:

1,3,4-oxadiazole; isoniazid; isonicotinic acid hydrazide; antimicrobial activity; disc diffusion

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ABSTRACT

A series of six 2-aryl-5-(pyridin-4-yl)-1,3,4-oxadiazoles (VD-1 to VD-6) was synthesized from isonicotinic acid. Isonicotinic acid was esterified, converted to isonicotinic acid hydrazide, and cyclized with six aromatic acids in phosphorus oxychloride. The compounds were obtained in 65–82% yield and characterized by melting point, TLC, IR, ^{1}H NMR, and mass spectrometry. We tested antimicrobial activity by disc diffusion against *Enterococcus faecalis, Bacillus subtilis, Serratia marcescens, Pseudomonas aeruginosa, Candida tropicalis,* and *Candida parapsilosis*, using ciprofloxacin and amphotericin B as standards. All compounds showed antibacterial activity, with zones of inhibition of 4–10 mm against 25–30 mm for ciprofloxacin. VD-1 and VD-6 were the most active against Gram-positive bacteria, and VD-5 against *P. aeruginosa*. Antifungal activity was lower: VD-3 and VD-4 were active against both *Candida* species, while VD-1 and VD-6 were inactive. The synthesized oxadiazoles showed moderate antimicrobial activity and can serve as leads for further development.

1. Introduction

Antimicrobial resistance is a major global health problem and caused an estimated 1.27 million deaths in 2019 [1]. Tuberculosis also remains a leading infectious cause of death, and drug-resistant strains make treatment harder [2]. New antimicrobial compounds are therefore needed.

Isoniazid (isonicotinic acid hydrazide) is a first-line antitubercular drug [3]. Its hydrazide group can be converted into heterocyclic rings, and this has been widely used to make new antimicrobial agents. The 1,3,4-oxadiazole ring is a stable five-membered heterocycle that is present in drugs such as raltegravir and zibotentan [4]. Its derivatives show antibacterial, antifungal, antitubercular, anti-inflammatory and anticancer activities [5,6].

Oxadiazole derivatives of isoniazid have shown antitubercular and antimicrobial activity [7–10]. Aryl substituents on 2,5-disubstituted oxadiazoles also affect antimicrobial activity [11–13]. In the present work, six 2-aryl-5-(pyridin-4-yl)-1,3,4-oxadiazoles were synthesized from isonicotinic acid, characterized, and screened for antibacterial and antifungal activity.

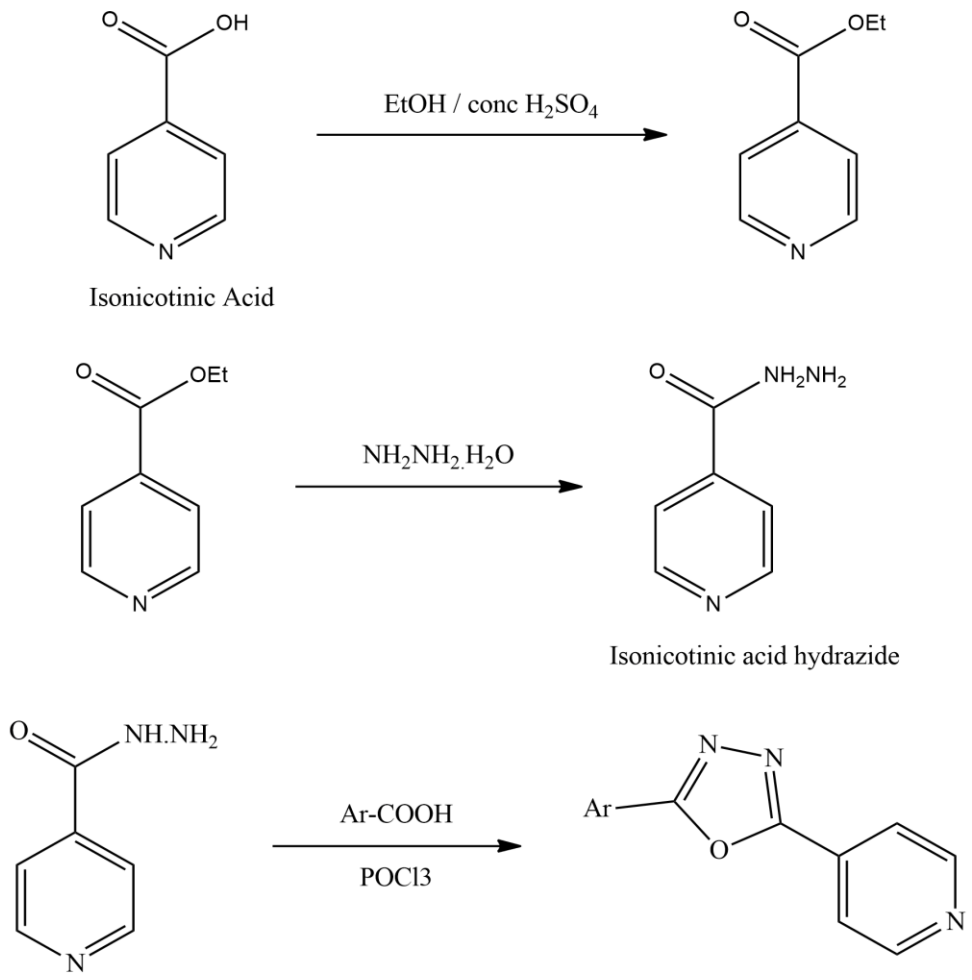
2. Materials and methods

2.1 Chemicals and instruments

All chemicals and solvents were of analytical grade. They were purchased from Central Drug House (New Delhi), HiMedia, Rankem, Thomas Baker, Thermo Fisher Scientific India and Avantor, and used without further purification. Reactions were monitored by TLC on pre-coated silica gel plates (Merck) using chloroform:methanol (8:2) as the mobile phase, with UV light and iodine vapour for detection. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrophotometer (KBr). ^{1}H NMR spectra were recorded on a JEOL spectrometer at 400 MHz in DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on a Waters UPLC-TQD mass spectrometer (ESI).

2.2 Synthesis

The compounds were synthesized in three steps (Scheme 1).



Scheme 1. Synthesis of 2-aryl-5-(pyridin-4-yl)-1,3,4-oxadiazoles (VD-1 to VD-6).

Step I: Ethyl isonicotinate. Isonicotinic acid (0.02 mol), absolute ethanol (0.20 mol) and concentrated sulfuric acid (1 mL) were refluxed until the reaction was complete (TLC). The cooled mixture was poured into ice-cold water (200 mL) and extracted with ether. The ether layer was washed with sodium bicarbonate solution and evaporated to give the ester as a liquid.

Step II: Isonicotinic acid hydrazide. Ethyl isonicotinate (0.01 mol) and hydrazine hydrate (0.01 mol) were refluxed in ethanol (5 mL) until the reaction was complete (TLC). The solid obtained was filtered, washed with cold water and recrystallized from ethanol (m.p. 169–171 °C).

Step III: 2-Aryl-5-(pyridin-4-yl)-1,3,4-oxadiazoles (VD-1 to VD-6). Isonicotinic acid hydrazide (0.01 mol) and the aromatic acid (0.01 mol) were mixed, and phosphorus oxychloride (5–7 mL) was added dropwise. The mixture was refluxed on a water bath at 100 °C for 10–12 h, cooled and poured onto crushed ice. It was neutralized with 20% sodium bicarbonate solution. The precipitate was filtered, washed with cold water and recrystallized from ethanol. The aromatic acids used were N-phenylanthranilic acid (VD-1), nicotinic

acid (VD-2), 3,5-dinitrosalicylic acid (VD-3), p-toluic acid (VD-4), cinnamic acid (VD-5) and gallic acid (VD-6).

2.3 Antimicrobial activity

Antimicrobial activity was tested by the Kirby–Bauer disc diffusion method [14,15]. The organisms were *E. faecalis* (MTCC 429), *B. subtilis* (MTCC 1133), *S. marcescens* (MTCC 86), *P. aeruginosa* (MTCC 3541), *C. tropicalis* (MTCC 1000) and *C. parapsilosis* (MTCC 998), obtained from MTCC, Chandigarh. Mueller–Hinton agar plates were inoculated with 100 µL of culture adjusted to 0.5 McFarland standard. Whatman No. 1 paper discs (5 mm) were loaded with 10 µL of the test compounds in DMSO at different concentrations (up to 100 mg/mL). DMSO was used as the vehicle control, and ciprofloxacin (10 µg) and amphotericin B (50 µg) as the standards. Plates were incubated at 37 °C for 24 h, and the zones of inhibition were measured in mm.

3. Results

3.1 Physical data

All six compounds were obtained as solids in 65–82% yield. Their physical data are given in Table 1.

Table 1. Physical data of the synthesized compounds

Code	Ar	Molecular formula	Mol. wt.	Yield (%)	m.p. (°C)	R*f*	Colour
VD-1	2-(phenylamino)phenyl	$C_{19}H_{14}N_4O$	314.35	79	168	0.72	Brick red
VD-2	pyridin-3-yl	$C_{12}H_8N_4O$	224.22	78	178	0.63	Yellow
VD-3	2-hydroxy-3,5-dinitrophenyl	$C_{13}H_7N_5O_6$	329.23	80	166	0.78	White
VD-4	4-methylphenyl	$C_{14}H_{11}N_3O$	237.26	72	182	0.68	White
VD-5	Styryl	$C_{15}H_{11}N_3O$	249.27	82	171	0.74	Yellow
VD-6	3,4,5-trihydroxyphenyl	$C_{13}H_9N_3O_4$	271.23	65	173	0.64	Dark brown

R*f* in chloroform:methanol (8:2). All compounds were soluble in methanol, ethanol, chloroform, acetone and DMSO.

3.2 Spectral data

VD-1: 2-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]-N-phenylaniline. IR (KBr, cm^{-1}): 3101 (Ar C–H), 1667 (C=N), 1475 (C=C), 1309 (C–N), 1162 (C–O–C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.75 (s, 3H), 7.93 (s, 3H), 7.68 (t, J = 7.6 Hz, 3H), 7.48 (d, J = 8.0 Hz, 3H), 7.29 (s, 3H). MS (ESI) m/z: 315.5 $[M+H]^+$.

VD-2: 2-(pyridin-3-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazole. IR (KBr, cm^{-1}): 3093 (Ar C–H), 1673 (C=N), 1514 (C=C), 1161 (C–O–C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.92 (s, 2H), 8.76 (s, 1H), 8.73 (t, J = 7.2 Hz, 2H), 8.66 (d, J = 7.6 Hz, 3H).

VD-3: 2,4-dinitro-6-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]phenol. IR (KBr, cm^{-1}): 3416 (O–H), 3059 (Ar C–H), 1640 (C=N), 1517 (N=O), 1202 (C–O–C). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.85 (d, J = 6.0 Hz, 1H), 8.02 (d, J = 6.0 Hz, 1H), 7.81 (t, J = 7.6 Hz, 2H), 7.47 (s, 3H).

VD-4: 2-(4-methylphenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazole. IR (KBr, cm^{-1}): 1677 (C=N), 1525 (C=C), 1415 (CH_3 bending), 1284 (C–O–C). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 8.01 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 4.4 Hz, 5H), 7.43 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 4H). MS (ESI) m/z: 238.0 $[M+H]^+$.

VD-5: 2-styryl-5-(pyridin-4-yl)-1,3,4-oxadiazole. IR (KBr, cm^{-1}): 3062 (C–H), 1672 (C=N), 1598 (C=C), 1269 (C–O–C). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 8.83 (s, 2H), 8.71 (s, 2H), 8.66 (d, J = 7.2 Hz, 2H), 8.59 (s, 3H), 7.93 (s, 2H). MS (ESI) m/z: 250.1 $[M+H]^+$.

VD-6: 5-[5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol. IR (KBr, cm^{-1}): 3266 (O–H), 1608 (C=N), 1523 (C=C), 1178 (C–O–C). ^1H NMR (400 MHz, DMSO-d_6) δ ppm: 8.76 (d, J = 6.0 Hz, 2H), 7.80 (d, J = 4.4 Hz, 2H), 7.71 (d, 2H), 7.34 (s, 3H).

3.3 Antimicrobial activity

The zones of inhibition are given in Table 2. DMSO showed no zone of inhibition.

Table 2. Zone of inhibition (mm) of the compounds; the effective amount (μg/disc) is given in brackets

Compound	*E. faecalis*	*B. subtilis*	*S. marcescens*	*P. aeruginosa*	*C. tropicalis*	*C. parapsilosis*
VD-1	10 (500)	10 (50)	6.7 (50)	7 (125)	–	–
VD-2	6 (125)	7.5 (50)	6.5 (50)	7 (50)	6 (125)	–
VD-3	4 (50)	7 (50)	7 (50)	7 (50)	6.5 (50)	6 (50)
VD-4	6 (50)	7 (50)	7 (50)	7 (50)	8 (50)	6.6 (50)
VD-5	6.7 (125)	8 (50)	6.3 (50)	8 (50)	6.5 (125)	2 (125)
VD-6	8 (50)	8 (50)	6 (50)	7 (50)	–	–
Ciprofloxacin	25 (10)	28 (10)	30 (10)	26 (10)	NT	NT
Amphotericin B	NT	NT	NT	NT	17 (50)	21.3 (50)

– = no zone up to 1000 μg/disc; NT = not tested.

4. Discussion

The 2-aryl-5-(pyridin-4-yl)-1,3,4-oxadiazoles were obtained in good yield by cyclization of isonicotinic acid hydrazide with aromatic acids in phosphorus oxychloride, a commonly used method for 2,5-disubstituted oxadiazoles [11,12]. The IR spectra showed C=N stretching at 1608–1677 cm^{-1} and C–O–C stretching at 1161–1284 cm^{-1}, which are characteristic of the 1,3,4-oxadiazole ring [16]. The ^1H NMR spectra showed aromatic protons of the pyridine and aryl rings at δ 7.29–8.92 ppm. Mass spectra of VD-1, VD-4 and VD-5 showed the expected $[M+H]^+$ peaks.

All compounds showed antibacterial activity against both Gram-positive and Gram-negative bacteria, but the activity was moderate compared with ciprofloxacin. VD-1 (diphenylamine) and VD-6 (trihydroxyphenyl) gave the largest zones against Gram-positive bacteria (8–10 mm). Against the Gram-negative bacteria, all compounds gave similar zones (6–8 mm), and VD-5 (styryl) was the most active against *P. aeruginosa*. Similar effects of aryl

substituents on antibacterial activity of oxadiazoles was reported earlier [11–13].

Antifungal activity was lower than antibacterial activity. VD-3 and VD-4 were active against both *Candida* species, while VD-1 and VD-6 were inactive up to 1000 µg/disc. Oxadiazole derivatives of isoniazid have also shown antitubercular activity [7–10], so these compounds may be worth testing against *Mycobacterium tuberculosis*. MIC determination would give a more exact measure of activity.

5. Conclusion

Six 2-aryl-5-(pyridin-4-yl)-1,3,4-oxadiazoles were synthesized from isonicotinic acid and characterized by IR, ^{1}H NMR and mass spectrometry. All compounds showed moderate antibacterial activity, and VD-3 and VD-4 also showed antifungal activity. These compounds can be used as leads for the development of new antimicrobial agents.

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Conflict of interest

The authors declare no conflict of interest.

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