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Synthesis and Biological Evaluation of 1,3,4-Oxadiazole Fused Pyridine Derivatives as Antibacterial and Antifungal Agents[1]

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Abstract—A series of novel 1,3,4-oxadiazole fused pyridine derivatives were synthesized **11a–11f** and their structures confirmed by IR, ^{1}H NMR and Mass spectral data. The compounds were evaluated for their antibacterial and antifungal activities against Gram negative and positive bacterial strains including *Escherichia coli* (MTCC 443), *K. Pneumoniae* (MTCC 109), *S.Aureus* (MTCC 96), *B. Subtilis* (MTCC 441) and *Sclerotium rolfsii, Macrophomina phaseolina.* Compounds **11d, 11e,** and **11f** demonstrated high antibacterial activity.

Keywords: nicotinic acid, isoniazid, furamizole, antibacterial activity

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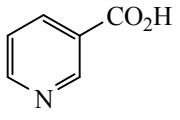
INTRODUCTION

Compounds with the pyridine backbone possess a variety of biological activities including antimicrobial [1], herbicidal [2], insecticidal [3], antiprion [4], antihepatitis B virus [5], antibacterial [6], and many others [7-9]. Some pyridine containing drugs such as Nicotinic acid (1) are used for treatment of cardiovascular disease [10]. Isoniazid (2) is used for tuberculosis [11] (Scheme 1).

Scheme 1.



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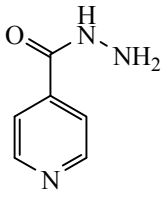

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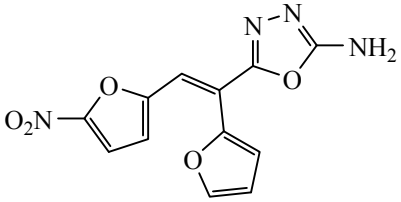

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1,3,4-Oxadiazole is another important five-member heterocyclic compound associated with potent pharmacological activity due to the presence of the –N=C–O– linkage [12].

In view of the above, we have synthesized a novel series of 1,3,4-oxadiazole incorporated pyridine derivatives **11a–11f**. The structures of products were confirmed by IR, ^{1}H NMR and mass spectra and their antibacterial and antifungal activities were evaluated.

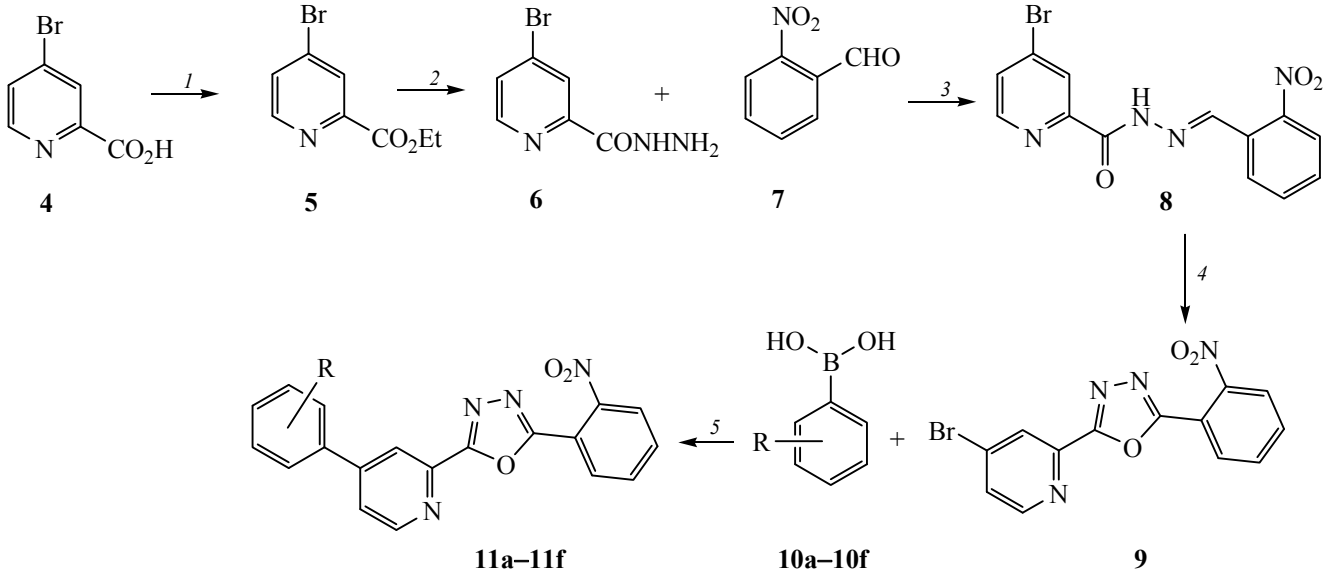
Synthesis of the compounds **11a–11f** is outlined in Scheme 2.

EXPERIMENTAL

All chemicals and reagents were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa, Johnson Matthey Company, Ward Hill, MA, USA) and used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualized by UV light or iodine vapor. Melting points were

[1] The text was submitted by the authors in English.

Scheme 2. Synthetic pathway to **11a–11f**.



R = H (**11a**), 3-OH (**11b**), 4-OMe (**11c**), 2-CF_3 (**11d**), 4-CN (**11e**), 3,4-difluoro (**11f**). Reagents and conditions: (*1*) Ethanol, conc H_2SO_4, reflux, 12 h. (*2*) Ethanol, $N_2H_4.H_2O$, reflux, 12 h. (*3*) Ethanol, reflux, 12 h. (*4*) (Diacetoxyiodo)benzene, CH_2Cl_2, 40°C, 12 h. (*5*) DME, H_2O, Na_2CO_3, $Pd(PPh_3)_4$, 100°C, 10 min.

determined with an electro thermal melting point apparatus. IR spectra were recorded on a Schimadzu-FT-IR Spectrophotometer in KBr discs. ^{1}H NMR spectra were measured at 400 MHz using TMS as the theinternal standard. ESI spectra were measured on Micro mass, Quattro LC using ESI^+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector.

Ethyl 4-bromopicolinate (5). To a stirred solution of 4-bromopicolinic acid **4** (20 g, 87.33 mmol) in ethanol (250 mL) cooled to 5°C, sulfuric acid (3 mL) was added and the reaction mixture was slowly cooled down to room temperature and then heated at 70°C for 12 h. Upon completion of the reaction (TLC), the solvent was evaporated under vacuum. The residue was dissolved in ethyl acetate (500 mL), washed with ice cold water (100 mL), saturated by sodium bicarbonate solution (100 mL) and brine solution (100 mL). The organic layer was separated and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and purified by column chromatography (hexane–ethyl acetate = 20 : 80) to give compound **5** (86%).

4-Bromopicolinohydrazide (6). To a stirred solution of ethyl 4-bromopicolinate **5** (15 g, 65.51 mmol) in ethanol (150 mL) was added hydrazine hydrate (6.55 g, 6.42 mL, 131.01 mmol). The reaction mixture was heated at 70°C for 12 h. Upon completion of the reaction (TLC), the solid precipitate was filtered off and dried under vacuum to give compound **6** (85%).

(*E*)-4-Bromo-*N*'-(2-nitrobenzylidene)picolinohydrazide (8). To a stirred solution of 4-bromopicolinohydrazide **6** (12 g, 55.82 mmol) in ethanol (120 mL) was added 2-nitrobenzaldehyde **7** (10.11 g, 66.99 mmol). The reaction mixture was heated at 70°C for 12 h. Upon completion of the reaction (monitored by TLC), the solid precipitate was filtered off and washed with *n*-hexane (50 mL), and dried under vacuum to give compound **8** (82%).

2-(4-Bromopyridin-2-yl)-5-(2-nitrophenyl)-1,3,4-oxadiazole (9). To a stirred solution of (*E*)-4-bromo-*N*'-(2-nitrobenzylidene) picolinohydrazide **8** (10 g, 28.73 mmol) in CH_2Cl_2 (100 mL) was added diacetoxy iodobenzene (13.87 g, 42.69 mmol). The reaction mixture was heated at 40°C for 12 h. Upon completion of the reaction (TLC), the mixture was diluted with DCM (200 mL) and washed with water (50 mL). The organic layer was separated and dried over anhydrous sodium sulfate, filtered and evaporated under vacuum to give compound **9** (80.5%).

Synthesis of 1,3,4-oxadiazole fused pyridine derivatives 11a–11f. To a stirred solution of 2-(4-bromopyridin-2-yl)-5-(2-nitrophenyl)-1,3,4-oxadiazole **9** (100 mg,

Table 1. Comparable studies of the Suzuki coupling reaction

Comp. no.	Conventional method		Microwave method	
	time, h	yield, %	time, min	yield, %
11a	10.00	51	20	75
11b	12.10	48	15	77
11c	14.30	55	10	83
11d	8.20	49	12	71
11e	9.30	56	30	80
11f	16.10	60	25	82

0.28 mmol) were added a substituted arylboronic acid **10a–10f** (1.2 equiv.) in 1,2-dimethoxy ethane (5 mL), water (2 mL), Na_2CO_3 (3 eq). The mixture was degassed with Ar within 10 min and $Pd(PPh_3)_4$ (0.05 equiv.) was added. The reaction mixture was heated at 100°C for an appropriate period of time. Upon completion of the reaction (TLC), the mixture was diluted with ethyl acetate (20 mL) and washed with water (2×5 mL). The organic layer was separated and dried over anhydrous sodium sulfate and the solvent evaporated under vacuum to give products **11a–11f**. The similar processes carried out under microwave irradiation using CEM microwave at 490 W led to higher overall yields (75–82%) of the products (Table 1).

2-(2-Nitrophenyl)-5-(4-phenylpyridine-2-yl)-1,3,4-oxadiazole (11a). Yield 75%, mp 150–152°C. IR spectrum, ν, cm^{-1}: 3432, 2925, 1531, 1348, 857, 727. ^{1}H NMR spectrum, δ, ppm: 7.64–7.54 m (3H), 7.93–8.03 m (5H), 8.20 d (J = 8.4 Hz, 1H), 8.26 d (J = 7.2 Hz, 1H), 8.51 s (1H), 8.87 d (J = 4.8 Hz, 1H). ESI-MS: m/z = 345 $[M + H]^+$.

3-(2-(5-(2-Nitrophenyl)-1,3,4-oxadiazol-2-yl)pyridin-4-yl) phenol (11b). Yield 77%, mp 145–150°C. IR spectrum, ν, cm^{-1}: 3209, 2923, 1601, 1535, 1365, 1220, 834, 719. ^{1}H NMR spectrum, δ, ppm: 6.95 d (J = 8.8 Hz, 1H), 7.26 s (1H), 7.41–7.33 m (1H), 7.53–7.65 m (2H), 8.26 d (J = 8.8 Hz, 2H), 8.19 d.d (J = 2.76 Hz, 2H), 8.42 s (1H), 8.85 d (J = 5.6 Hz, 1H), 9.81 s (1H). ESI-MS: m/z = 361.15 $[M + H]^+$.

2-(4-(3-Methoxyphenyl)-pyridine-2-yl)-5-(2-nitrophenyl)-1,3,4-oxadiazole (11c). Yield 83%, mp 201–205°C. IR spectrum, ν, cm^{-1}: 3445, 2935, 1597, 1540, 1365, 1256, 828, 573. ^{1}H NMR spectrum, δ, ppm: 3.85 s (3H), 7.13 d (J = 8.8 Hz, 2H), 7.91–8.03 m (5H), 8.19 d (J = 8.4 Hz, 1H), 8.26 d (J = 8.4 Hz, 1H), 8.46 s (1H), 8.80 d (J = 5.2 Hz, 1H). ESI-MS: m/z = 375.20 $[M + H]^+$.

Table 2. Antibacterial activity of compounds **11a–11f**

Compound	Gram negative		Gram positive	
	E.Coli MTCC 443	*K. Pneumoniae* MTCC 109	*S.Aureus* MTCC 96	*B. Subtilis* MTCC 441
	Zone of inhibition, mm			
11a	6	–	8	12
11b	7	10	12	14
11c	8	12	10	13
11d	9	14	12	16
11e	12	13	13	18
11f	10	14	13	16
Gentamycin	15	22	15	20

4-[2-(Trifluoromethyl)phenyl]-2-[5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl]pyridine (11d). Yield 71%, mp 195–200°C. IR spectrum, ν, cm^{-1}: 3434, 3085, 1551, 1529, 1353, 1316, 1170, 1118, 854, 775. ^{1}H NMR spectrum, δ, ppm: 7.58 d (J = 7.6 Hz, 1H), 7.70 d (J = 4.8 Hz, 1H), 7.76 t (J = 7.6 Hz, 1H), 7.84 t (J = 7.6 Hz, 1H), 7.94–8.02 m (3H), 8.16–8.20 m (2H), 8.25 d.d (J = 1.6,7.2 Hz, 1H), 8.91 d (J = 5.2 Hz, 1H). ESI-MS: m/z = 412.9 $[M + H]^+$.

4-{2-[5-(2-Nitrophenyl)-1,3,4-oxadiazol-2-yl]pyridin-4-yl}benzonitrile (11e). Yield 80%, mp 165–170°C.

Table 3. Anti-fungal activity of target compounds **11a–11f**

Compound	Zone of inhibition, cm	
	Sclerotium rolfsii	*Macrophomina phaseolina*
11a	0.1	0.2
11b	0.2	0.1
11c	0.2	0.2
11d	0.3	0.2
11e	0.1	0.3
11f	0.3	0.2
Mancozeb	0.4	0.4

IR spectrum, ν, cm^{-1}: 3409, 2919, 2228, 1599, 1363, 830. ^1H NMR spectrum, δ, ppm: 7.96–8.27 m (9H), 8.56 s (1H), 8.93 d (J = 5.2 Hz, 1H). ESI-MS: m/z = 369.9 $[M + H]^+$.

4-(3,4-Difluorophenyl)-2-[5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl]pyridine (11f). Yield 82%, mp 135–140°C. IR spectrum, ν, cm^{-1}: 3855, 3422, 2920, 2228, 1599, 1537, 1363, 830, 725. ^1H NMR spectrum, δ, ppm: 7.62–7.69 m (1H), 7.87 m (1H), 7.96–8.06 m (3H), 8.13–8.21 m (2H), 8.27 d (J = 7.6 Hz, 1H), 8.55 s (1H), 8.8 d (J = 4.8 Hz, 1H). ESI-MS: m/z = 380.9 $[M + H]^+$.

Antibacterial activity. The compounds **11a–11f** were evaluated for their antibacterial activity against both Gram nagative and positives bacterial strains including *Escherichia coli* (MTCC 443), *K. Pneumoniae* (MTCC 109) and *S.Aureus (*MTCC 96), *B. Subtilis* (MTCC 441) (Table 2). Gentamycin was used as the control. Compounds **11d**, **11e**, and **11f** demonstrated high activity.

Anti-fungal activity. The compounds **11a–11f** were screened *in vitro* for anti-fungal activity against two fungal strains, *Sclerotium rolfsii and Macrophomina phaseolina,* using Mancozeb as the standard control drug (Table 3). Compounds **11d, 11e,** and **11f** demonstrated high activity.

CONCLUSIONS

A novel series of 1,3,4-oxadiazole fused pyridine derivatives **11a–11f** was synthesized and the structures were confirmed by IR, ^1H NMR and Mass spectra. All derivatives were evaluated for their antibacterial and antifungal activities against Gram nagative and positives bacterial strains, including *Escherichia coli* (MTCC 443), *K. Pneumoniae* (MTCC 109), *S.Aureus (*MTCC 96), *B. Subtilis* (MTCC 441) and *Sclerotium rolfsii, Macrophomina phaseolina.* Compounds **11d**, **11e,** and **11f** demonstrated high antibacterial activity.

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