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Synthesis and Antitubercular Activity of Novel 1,3,4-Oxadiazole and 1,3,4-Thiadiazole Derivatives

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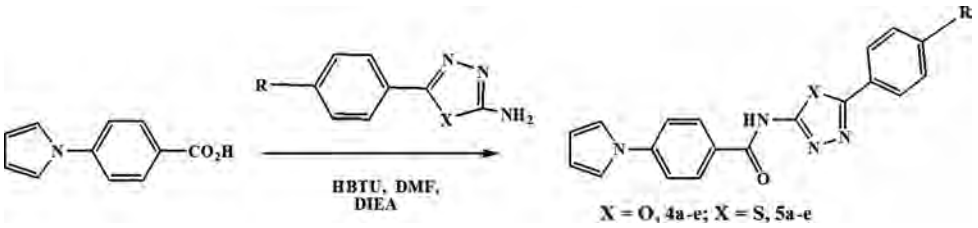
ABSTRACT Oxadiazole pyrrolyl benzamide derivatives **(4a-e)** and thiadiazole pyrrolyl benzamide derivatives **(5a-e)** were synthesized by the reaction of 4-(1*H*-pyrrol-1-yl)benzoic acid with *N*-(5-(4-substituted phenyl)-1,3,4-oxadiazole-2-amines and *N*-(5-(4-substituted phenyl)-1,3,4-thiadiazole-2-amines, respectively, in *N'*, *N'*-dimethyl formamide using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate as amide coupling agent and *N'*, *N'*-Diisopropylethylamine as a catalyst. All the newly synthesized compounds **(4a-e/5a-e)** were screened for *in vitro* antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$, and compounds **4c**, **4d**, **5c**, and **5d** have exhibited significant minimum inhibitory concentration values.



KEY WORDS Oxadiazoles, Thiadiazoles, 2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, *N'*,*N'*-Diisopropylethylamine, *N'*, *N'*-Dimethyl formamide, *Mycobacterium tuberculosis* $H_{37}Rv$, Antitubercular activity.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), and it is a most productive infectious agent affecting humans and it is second leading illness causing the death along with HIV.[1] According to the WHO report, in 2015, about 10.4 million new TB cases were seen worldwide, of which 56% were men, 34% were women, and 10% were children. People coinfected with HIV accounted for 1.2 million new TB cases, and only about 1.5% decline in TB cases were observed in 2014 and 2015. Therefore, there is a need to accelerate the rate of annual decline by 4–5% by 2020 to reach the first milestones of the end TB strategy. In recent years, there is an emergence of multidrug-resistant TB and also emergence of rifampicin-resistant TB. There were an estimated 1.4 million TB deaths in 2015 and an additional 0.4 million deaths resulting from TB cases coinfected with HIV. Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015.[1]

Pyrrole derivatives are important biological agents, and a extensive amount of research activity has been directed toward this class of compounds. In particular, they are used as antibacterial, antifungal, antiviral, antiproliferative, and antitubercular agents.[2-5] Some of these compounds have

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also antidepressant and analgesic properties.[6,7] Moreover, pyrroles have played a vibrant part in the development of the theory of heterocyclic combinations, and also, they are used extensively in organic synthesis.[8] A classical synthesis of 5-phenyl-1,3,4-oxadiazol-2-yl)-4-(1*H*-pyrrol-1-yl)benzamide and 5-phenyl-1,3,4-thiadiazol-2-yl)-4-(1*H*-pyrrol-1-yl) benzamide compounds involves the acid-catalyzed coupling reaction of substituted amines and aromatic acids to give *N*'-substituted pyrrolyl oxadiazole/thiadiazole benzamides.[9-12] In recent years, a significant portion of research in heterocyclic chemistry has been dedicated to develop pyrrolyl benzamides containing different aryl groups, as evident from the literature.[13-16] Pyrrole is also a significant part of macrocyclic porphyrin ring system of chlorophyll and hemin.[17] Apart from these properties, pyrrole and its derivatives possess a number of biological activities such as antitumor,[18] antibacterial,[19] anti-inflammatory,[20] analgesic,[21] anticonvulsant,[22] antitubercular,[23,24] antihypertensive,[25] and antiviral.[26]

From the literature survey, it was found that pyrroles, pyrrolyl oxadiazoles, and thiadiazoles are important to possess many pharmacological activities, this prompted us to synthesize new *N*-substituted(5-phenyl-1,3,4-oxadiazol-2-yl)-4-(1*H*-pyrrol-1-yl)benzamide and *N*-substituted(5-phenyl-1,3,4-thiadiazol-2-yl)-4-(1*H*-pyrrol-1-yl)benzamide derivatives and screen them for antitubercular activity.

RESULTS AND DISCUSSION

Earlier, we have reported some of the substituted pyrrolyl 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives and they were found to possess more potent antimycobacterial activity,[9,10,13,14] and in continuation of our work herein, we report some of the N-substituted pyrrolyl 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives (**4a-e/5a-e**). 4-(1*H*-pyrrol-1-yl)benzoic acid (**1**) and *N*-(5-(4-substituted phenyl)-1,3,4-oxadiazole-2-amines/*N*-(5-(4-substituted phenyl)-1,3,4-thiadiazole-2-amines (**2a-e/3a-e)** were synthesized according to the literature procedure reported by us.[13,14] Acid **1** was made to react with 1,3,4-oxadiazole-2-amines (**2a-e**) and 1,3,4-thiadiazole-2-amines (**3a-e)** in the presence of 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and *N*',*N*'-Diisopropylethylamine (DIEA) to yield titled compounds **4a-e** and **5a-e**, respectively [**Scheme 1**]. The structures of all the synthesized compounds were established on the basis of their analytical and spectral data. The physicochemical data for all synthesized compounds are compiled in **Table 1**.

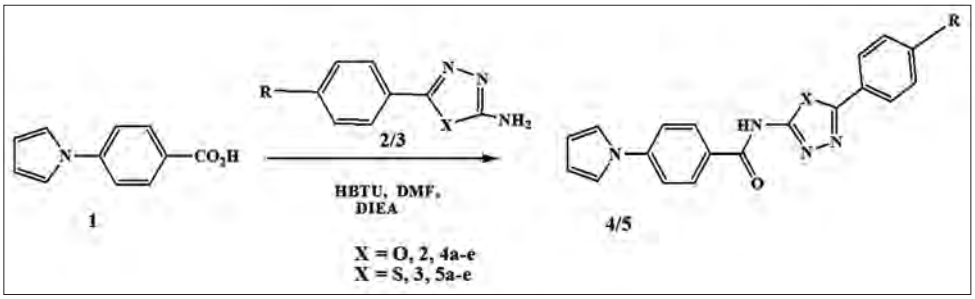
The IR spectrum of compound **4a** exhibited a strong stretching band at 3211 cm^{-1} due to the presence of -NH, peaks at 1670 and 1279 cm^{-1} were due to C = O and C-O-C group, respectively, and aromatic stretching was observed at 2918 cm^{-1}. Further, the structure of *N*-(5-phenyl-1,3,4-oxadiazol-2-yl)-4-(1*H*-pyrrol-1-yl)benzamide was confirmed by ^{1}H nuclear magnetic resonance (NMR), wherein 4 protons of pyrrole ring resonated as a pair of doublet at δ 7.37 and 6.31 ppm. Ten protons of phenyl and another bridging phenyl ring were resonated as multiplet at δ 7.38–8.17 ppm. The IR spectrum of compound **5a** showed a strong stretching band at 3141 cm^{-1} due to the presence of -NH, peaks at 1764 were due to C = O group, and aromatic stretching was observed at 2923 cm^{-1}. Wherein 4 protons of pyrrole ring resonated as a pair of doublet at δ 7.58 and 6.63 ppm in ^{1}H NMR spectrum. Ten protons of phenyl and another bridging phenyl ring were resonated as a multiplet at δ 7.32–8.29 ppm.

The additional support for the structure of compound **4a** and **5a** was obtained by recording their mass spectra (MS) which showed a molecular ion peak at m/z 331.16 (M^+) and 346.16 (M^+), respectively, corresponding to their molecular weight.

Antitubercular activity was determined for all new compounds (**4a-e/5a-e**) against *M. tuberculosis* strain H_{37}Rv using Microplate Alamar Blue assay (MABA) method using pyrazinamide and isoniazid as reference drugs, and the results are depicted in **Table 2**. The preliminary anti-tubercular

Table 1: Physical data of synthesized compounds

Compound number	Molecular formula	M.P.°C	Yield %
4a	$C_{19}H_{14}N_4O_2$	148–150	70
4b	$C_{19}H_{13}FN_4O_2$	140–142	68
4c	$C_{19}H_{13}ClN_4O_2$	170–172	60
4d	$C_{19}H_{13}BrN_4O_2$	156–158	77
4e	$C_{20}H_{16}N_4O_2$	160–164	80
5a	$C_{19}H_{14}N_4OS$	180–182	75
5b	$C_{19}H_{13}FN_4OS$	190–192	80
5c	$C_{19}H_{13}ClN_4OS$	210–212	50
5d	$C_{19}H_{13}BrN_4OS$	232–234	60
5e	$C_{20}H_{16}N_4OS$	260–264	56



Scheme 1: Synthetic route for benzamide compounds containing pyrrole

screening revealed that majority of compounds showed a good activity. The activities of compounds (**4a-e/5a-e**) are expressed in terms of minimum inhibitory concentration (MIC) values. Compounds **5c, 5d, 5c,** and **5d** showed better antitubercular activity.

EXPERIMENTAL SECTION

Melting points were determined using the Shital-digital programmable melting point apparatus and are uncorrected. Fourier transform-infrared (FTIR) spectra in KBr pellets were recorded on a Bruker FTIR spectrophotometer. The ^{1}H NMR spectra were recorded on a Bruker AVANCE II at 400/100 MHz, and chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane. The abbreviations used to describe the peak patterns are as follows: (s) Singlet, (d) doublet, (t) triplet, (dd) doublet of doublet, and (m) multiplet. MS were recorded in a JEOL GCMATE II GC-mass spectrometer and Shimadzu QP 20105 GC-mass spectrometer. Analytical thin-layer chromatography (TLC) was performed on precoated TLC sheets of silica gel 60 F_{254} (Merck, Darmstadt, Germany) visualized by long- and short-wavelength ultraviolet lamps/iodine vapors.

General procedure for the synthesis of *N*-(5-(4-substituted phenyl)-1,3,4-oxadiazol-2-yl)-4-(1*H*-pyrrol-1-yl)benzamides 4(a-e)/*N*-(5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl)-4-(1*H*-pyrrol-1-yl) benzamides 5(a-e)

0.0018 mol of 5-phenyl-1, 3, 4-oxadiazol-2-amines/5-phenyl-1, 3, 4-thiadiazol-2-amines and 0.0019 mol of 4-(1*H*-pyrrol-1-yl) benzoic acid were dissolved in dry *N*', *N*'-dimethyl formamide (20 mL), and HBTU (0.0023 mol) and DIEA (0.0053 mol) were added and stirred for 5-24 h at room temperature. The reaction mixture was monitored by TLC (chloroform:methanol, 9:1). The solution mixture was quenched by brine. The resulting mixture was extracted with ethyl acetate (3 × 50 mL). The ethyl acetate layer was washed with 1N HCl, then with saturated sodium hydrogen carbonate solution followed by brine, then evaporated to solid, and crude product was purified by column chromatography on silica gel with ethyl acetate:petroleum ether (1:9) as eluent to yield *N*-(5-(4-substituted phenyl)-1,3,4-oxadiazol-2-yl)-4-(1*H*-pyrrol-1-yl)benzamides **4(a-e)** and *N*-(5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl)-4-(1*H*-pyrrol-1-yl)benzamides **5(a-e),** respectively.

Table 2: Preliminary *in vitro* antitubercular activity screen results of newly synthesized compounds

Compound	MIC values (μg mL^{-1}) *M. tuberculosis* $H_{37}Rv$
4a	50
4b	6.25
4c	3.12
4d	3.12
4e	25
5a	50
5b	6.25
5c	3.12
5d	3.12
5e	25
Pyrazinamide	3.12
INH	0.25

MIC: Minimum inhibitory concentration, *M. tuberculosis: Mycobacterium tuberculosis*

N-(5-Phenyl-1,3,4-oxadiazol-2-yl)-4-(1H-pyrrol-1-yl) benzamide (4a)

IR (KBr) ν_{max}, cm^{-1}: 3211 (NH Str), 2918 (Ar-C=C), 1670 (C=O), 1279 (C-O-C); ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.37 (d, 2H, *J* = 5.2 Hz, pyrrole-C_2, C_5-H), 6.31(d, 2H, *J* = 5.3 Hz, pyrrole-C_3 and C_4-H), 7.38-8.17 (m, 10H, phenyl-C_2, C_3, C_4, C_5, C_6-H bridging phenyl-C_2, C_3, C_5, C_6-H, NH); mass (m/z): 331.16 (M^+).

N-(5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl)-4-(1H-pyrrol-1-yl)benzamide (4b)

IR (KBr) ν_{max}, cm^{-1}: 3234 (NH Str), 3023 (Ar-C=C), 1686 (C=O), 1276 (C-O-C); mass (m/z): 348.38 (M^+).

N-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-4-(1H-pyrrol-1-yl)benzamide (4c)

IR (KBr) ν_{max}, cm^{-1}: 3428 (NH Str), 2980 (Ar-C=C), 1643 (C=O) and 1270 (C-O-C); mass (m/z): 364.38 (M^+), 365.08 (M^++1), 366.07 (M^++2).

N-(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl)-4-(1H-pyrrol-1-yl)benzamide (4d)

IR (KBr) ν_{max}, cm^{-1}: 3246 (NH Str), 2974 (Ar-C=C), 1677 (C=O) and 1278 (C-O-C); mass (m/z): 409.33 (M^+), 410.02 (M^++1), 411.05 (M^++2).

4-(1H-Pyrrol-1-yl)-N-(5-(p-tolyl)-1,3,4-oxadiazol-2-yl) benzamide (4e)

IR (KBr) ν_{max}, cm^{-1}: 3230 (NH Str), 3068 (Ar-C=C), 1637 (C=O) and 1274 (C-O-C); Mass (m/z): 343.38 (M^+).

N-(5-Phenyl-1,3,4-thiadiazol-2-yl)-4-(1H-pyrrol-1-yl) benzamide (5a)

IR (KBr) ν_{max}, cm^{-1}: 3141 (NH Str), 2923 (Ar-C=C), 1664 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.58, (d, 2H, *J* = 5.1 Hz, pyrrole-C_2, C_5-H), 6.33 (d, 2H, *J* = 5.3 Hz, pyrrole-C_3 and C_4-H), 7.32–8.29 (m, 10H, phenyl-C_2, C_3, C_4, C_5, C_6-H, bridging phenyl-C_2, C_3, C_5, C_6-H, NH); mass (m/z): 346.16 (M^+).

N-(5-(4-Fluorophenyl)-1,3,4-thiadiazol-2-yl)-4-(1H-pyrrol-1-yl)benzamide (5b)

IR (KBr) ν_{max}, cm^{-1}: 3399 (NH Str), 2919 (Ar-C=C), 1664 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.46, (d, 2H, *J* = 5.1 Hz, pyrrole-C_2, C_5-H), 6.33 (d, 2H, *J* = 5.2 Hz, pyrrole-C_3 and C_4-H), 7.21–8.17 (m, 9H, phenyl-C_2, C_3, C_5, C_6-H, phenyl-C_2, C_3, C_5, C_6-H, NH).

N-(5-(4-Chlorophenyl)-1,3,4-thiadiazol-2-yl)-4-(1H-pyrrol-1-yl)benzamide (5c)

IR (KBr) ν_{max}, cm^{-1}: 3283 (NH Str), 2929 (Ar-C=C), 1606 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 7.48, (d, 2H, *J* = 5.2 Hz, pyrrole- C_2, C_5-H), 6.33 (d, 2H, *J* = 5.3 Hz,

pyrrole-C_3 and C_4-H), 7.33–8.13(m, 9H, phenyl-C_2, C_3, C_5, C_6-H, bridging phenyl-C_2, C_3, C_5, C_6-H, NH).

N-(5-(4-Bromophenyl)-1,3,4-thiadiazol-2-yl)-4-(1H-pyrrol-1-yl)benzamide (5d)

IR (KBr) ν_{max}, cm^{-1}: 3140 (NH Str), 2917 (Ar-C=C), 1663 (C=O); ^1H NMR (DMSO-d_6, 400 MHz, δ): 7.54, (d, 2H, *J* = 5.1 Hz, pyrrole-C_2, C_5-H), 6.32 (d, 2H, *J* = 5.3 Hz, pyrrole-C_3 and C_4-H), 7.34–8.22 (m, 9H, phenyl-C_2, C_3, C_5, C_6-H, bridging phenyl-C_2, C_3, C_5, C_6-H, NH).

4-(1H-Pyrrol-1-yl)-N-(5-(p-tolyl)-1,3,4-thiadiazol-2-yl) benzamide (5e)

IR (KBr) ν_{max}, cm^{-1}: 3214 (NH Str), 3023 (Ar-C=C), 1681 (C=O).

Antitubercular activity

MIC values were determined for the newly synthesized compounds against *M. tuberculosis* strain H_{37}Rv using the MABA[27] using pyrazinamide as the standard drug. The 96 wells plate received 100 µl of Middlebrook 7H9 broth, and serial dilution of compounds was made directly on the plate with drug concentrations of 0.2, 0.4, 0.8, 1.6, 3.125, 6.25, 12.5, 25, 50, and 100 µg/mL. Plates were covered and sealed with parafilm and incubated at 37°C for 5 days. Then, 25 µl of freshly prepared 1:1 mixture of Almar blue reagent and 10% Tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth and pink color was scored as growth. The MIC was defined as the lowest drug concentration, which prevented color change from blue to pink and the results are depicted in **Table 2.**

CONCLUSION

In the present work, we have developed novel chemical entities as potential antitubercular agents. A series *N*-(5-(4-substituted phenyl)-1,3,4-oxadiazol-2-yl)-4-(1*H*-pyrrol-1-yl)benzamide and *N*-(5-(4-substituted phenyl)-1,3,4-thiadiazol-2-yl)-4-(1*H*-pyrrol-1-yl)benzamide derivatives were prepared and tested for the inhibition of *M. tuberculosis* growth. The *in vitro* study suggests that compounds **4c, 4d, 5c,** and **5d** are the most active with a MIC value of 3.12 µg/mL in the series. Due to the ability of these new compounds to sturdily affect *M. tuberculosis* growth, they could represent new leads for the development of candidate drugs.

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