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Oxadiazole mannich bases: Synthesis and antimycobacterial activity

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Abstract—A series of oxadiazole mannich bases were synthesized by reacting oxadiazole derivatives, dapsone and appropriate aldehyde in the presence of methanol. The synthesized compounds were evaluated for antimycobacterial activity against *M. tuberculosis* $H_{37}Rv$ and INH resistant *M. tuberculosis*. Among the synthesized compounds, compound (**4**) 3-{2-furyl[4-(4-{2-furyl [5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3-yl]methylamino}phenylsulfonyl)anilino]methyl}-5-(2-naphthyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione was found to be the most promising compound active against *M. tuberculosis* $H_{37}Rv$ and isoniazid (INH) resistant *M. tuberculosis* with Minimum inhibitory concentration (MIC) 0.1 μM & 1.10 μM respectively.

Among infectious diseases, tuberculosis (TB) is the number one killer with over two million casualties annually worldwide. The WHO considers tuberculosis to be the most dangerous chronic communicable disease in the world.[1] The emergence of AIDS, decline of socioeconomic standards and a reduced emphasis on tuberculosis control programmes contribute to the disease's resurgence in industrialized countries.[2] Resistance of *Mycobacterium tuberculosis* strains to antimycobacterial agents is an increasing problem worldwide.[3–5] In spite of severe toxicity on repeated dosing of isoniazid (INH) it is still considered to be a first line drug for chemotherapy of tuberculosis.[6] Literature survey reveals oxadiazole derivatives, which belong to an important group of heterocyclic compounds, have been the subject of extensive study in the recent past. Numerous reports have highlighted their chemistry and use.[7–9] Diverse biological activities, such as antimycobacterial, antiinflammatory, analgesic, antipyretic and anticonvulsant, have been associated with oxadiazole derivatives.[10,11] The current work describes the synthesis of novel oxadiazole-substituted mannich bases with encouraging antimycobacterial activity.

3-[2-Furyl(4-{4-[2-furyl(5-substituted phenyl-2-thioxo-2, 3-dihydro-1,3,4-oxadiazol-3-yl)methylamino]phenylsulfonyl}anilino)methyl]-5-(substituted phenyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (**1**–**7**) and 5-(substituted phenyl)-3-phenyl{4-[4-phenyl(5-substituted phenyl-2-thi oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)methylamino-phenylsulfonyl]anilino}methyl-2,3-dihydro-1,3,4-oxadiazole-2-thione (**8-14**) described in this study are shown in Table 1 and a reaction sequence for the preparation is outlined in Schemes 1 and 2 using the synthetic procedure based on the ring closure reaction of appropriate acid hydrazide with carbondisulfide (CS_2). All synthesized oxadiazole underwent condensation with appropriate aromatic aldehyde and dapsone in methanolic solution (reaction time varies from 8 to 22 h) affording titled mannich bases (**1**–**14**) in 72–92% yield after recrystallization with ethanol. The purity of the compounds was checked by TLC and elemental analyses. Both analytical and spectral data (^{1}H NMR, IR) of all the synthesized compounds were in full agreement with the proposed structures. In general, Infrared spectra (IR) revealed NH, C=N, C–N, S=O, C–O–C, C=S peak at 3400, 1600, 1350, 1250,1150 and 1100 cm^{-1}, respectively. In the Nuclear Magnetic Resonance spectra (^{1}H NMR) the signals of the respective protons of the prepared titled compounds were verified on the basis of their chemical shifts, multiplicities and coupling constants. The spectra showed a singlet at δ 6.16 ppm corresponding to CH proton; multiplet at δ 6.51–7.0 ppm

Keywords: Antimycobacterial activity; Dapsone; Mannich bases; Oxadiazole; Isoniazid.
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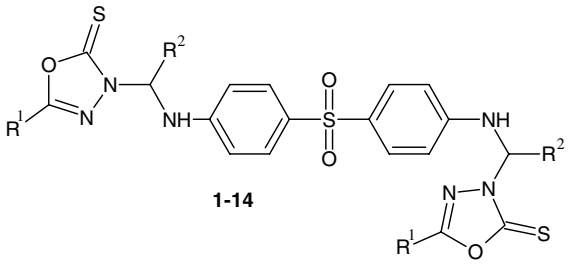
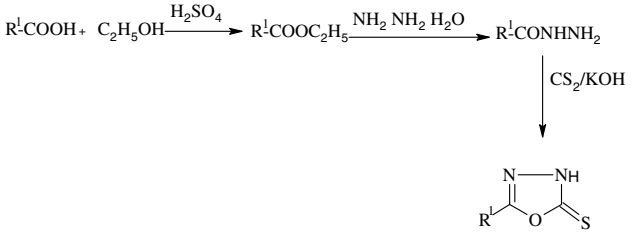
Table 1. Physical constants and antimycobacterial activity of the synthesized compounds



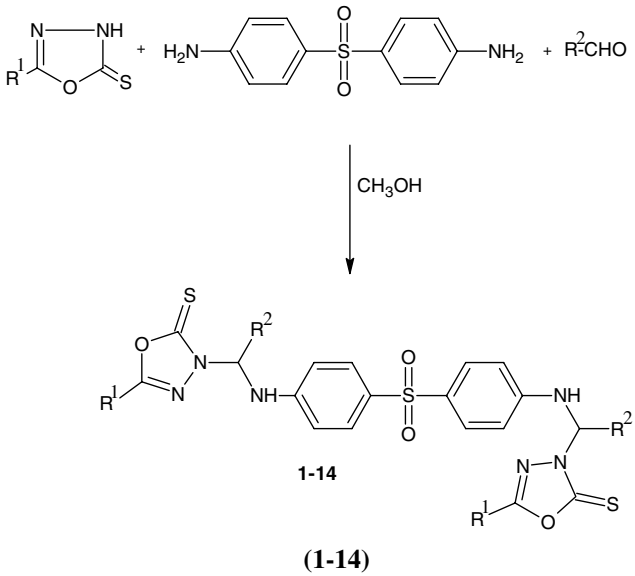
1-14

Compound	R^1	R^2	MP (°C)	Mol. Formula	Mol. wt	% yield	MIC (μM)	
							MTB[a]	MTB[b]
1	C_6H_5	Furfuryl–	265–267	$C_{38}H_{28}N_6O_6S_3$	760.86	92	0.94	2.24
2	4-NO_2–C_6H_5	Furfuryl–	292–294	$C_{38}H_{26}N_8O_{10}S_3$	850.85	90	0.42	1.74
3	C_6H_5–NH–C_6H_5	Furfuryl–	234–236	$C_{50}H_{38}N_8O_6S_3$	943.08	88	0.66	1.86
4	β-$C_{10}H_7$–O–CH_2	Furfuryl–	278–280	$C_{48}H_{36}N_6O_8S_3$	921.02	82	0.10	1.10
5	α-$C_{10}H_7$–O–CH_2	Furfuryl–	203–205	$C_{48}H_{36}N_6O_8S_3$	921.02	85	0.72	2.12
6	$C_6H_5OCH_2$	Furfuryl–	254–256	$C_{40}H_{32}N_6O_8S_3$	820.91	75	0.14	1.14
7	$C_6H_5CH_2$	Furfuryl–	211–213	$C_{40}H_{32}N_6O_6S_3$	788.91	72	0.24	3.24
8	C_6H_5	Phenyl–	221–223	$C_{42}H_{32}N_6O_4S_3$	780.93	80	1.72	5.42
9	4-NO_2–C_6H_5	Phenyl	282–284	$C_{42}H_{30}N_8O_4S_3$	870.93	76	1.94	3.94
10	C_6H_5–NH–C_6H_5	Phenyl	236–238	$C_{54}H_{42}N_8O_6S_3$	963.15	84	1.65	4.65
11	β-$C_{10}H_7$–O–CH_2	Phenyl	239–241	$C_{52}H_{40}N_6O_6S_3$	941.10	85	0.42	2.42
12	α-$C_{10}H_7$–O–CH_2	Phenyl	254–256	$C_{52}H_{40}N_6O_6S_3$	941.10	72	0.96	5.96
13	$C_6H_5OCH_2$	Phenyl	257–259	$C_{44}H_{36}N_6O_6S_3$	840.98	90	0.98	4.98
14	$C_6H_5CH_2$	Phenyl	244–246	$C_{44}H_{36}N_6O_4S_3$	808.98	92	1.29	5.98
INH	—	—	—	—	—	—	0.73	11.37

[a] *Mycobacterium tuberculosis* $H_{37}R_v$.
[b] INH resistant *Mycobacterium tuberculosis.*



Scheme 1.



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(1-14)

Scheme 2. Protocol for synthesis of titled compounds.

corresponding to furan protons; multiplet at δ 6.81–8.21 ppm for aromatic protons; singlet at δ 10.23 ppm corresponding to NH proton. The elemental analysis results were within ±0.4% of the theoretical values.

The synthesized compounds (**1**–**14**) were tested for their antimycobacterial activity in vitro against MTB and INHR-MTB by agar dilution method using double dilution technique similar to that recommended by the National Committee for Clinical Laboratory Standards[12] for the determination of minimum inhibitory concentration (MIC). The INHR-MTB clinical isolate was obtained from Tuberculosis Research Center, Chennai, India. The MIC was defined as the minimum concentration of compound required to inhibit 90% of bacterial growth and MIC's of the compounds are reported in Table 1 with standard drug INH for comparison. Among the newly synthesized compounds eleven compounds exhibited excellent antimycobacterial activity with MIC ranging from 0.1 to 5.96 μM. Among the synthesized compounds, 3-{2-furyl[4-(4-{2-furyl[5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3-yl]methylamino}phenylsulfonyl)anilino]methyl}-5-(2-naphthyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (**4**) was found to be most potent compound and was 7.3-fold against MTB and 10.3-fold against INH resistant MTB more active than isoniazid. These antimycobacterial data clearly show that the presence of furfuryl with 2-naphthoxymethyl substitution at mannich bases causes remarkable improvement in antitubercular activity against both *M. tuberculosis* $H_{37}Rv$ and INH resistant *M. tuberculosis*.

All the newly synthesized compounds (**1**–**14**) were further examined for toxicity (IC_{50}) in a mammalian Vero cell line at concentrations of 62.5 μg/mL. After 72 h exposure, viability was assessed on the basis of cellular conversion of (MTT) 3-(4,5-dimethylthiozole-2yl)-2,5-diphenyl tetrazolium bromide into a formazan product using the Promega Cell Tier 96 non-radioactive cell proliferation assay.[13] These compounds were found to be non-toxic at 62.5 μg/mL.

To summarize, we have synthesized new class of mannich bases as a novel class of antitubercular agents. The newly synthesized novel heterocycles exhibited promising mycobacterial activities against both drug-sensitive and drug-resistant strains of *Mycobacterium tuberculosis*. Among the compounds (**4**) 3-{2-furyl[4-(4-{2-furyl[5-(2-naphthyloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3-yl]methylamino}phenylsulfonyl)anilino]methyl}-5-(2-naphthyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione and (**6**) 3-[2-Furyl(4-{4-[2-furyl(5-phenoxymethyl-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)methylamino]phenylsulfonyl} anilino)methyl]-5-phenoxymethyl-2,3-dihydro-1,3,4-oxadiazole-2-thione[14] were most active agents and more than 5-fold potent than INH against *M. tuberculosis* $H_{37}Rv$ and ~10-fold potent than INH against INH resistant *M. tuberculosis*. These results make novel oxadiazole-substituted mannich bases interesting lead molecule for more synthetic and biological evaluation. It can be concluded that this class of compounds certainly hold great promise towards pursuit to discover novel class of antimycobacterial agents. Further studies to acquire more information about quantitative structure–activity relationships are in progress in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.04.004.

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14. **Compounds**: (**4**) IR:(KBr) cm-1: 3400 (NH), 1600 (C=N), 1350(C-N), 1250 (S=O), 1150 (C–O–C), 1100 (C=S);^{1}H NMR(DMSO-d_6) ppm: 4.72(4H, s, $CH_2 \times 2$), 6.10 (2H, s, CH×2), 6.38 (furan, m, 6H), 6.51–7.97 (22H, m, Ar), 10.42 (2H, s, NH×2); Ana $C_{48}H_{36}N_6O_8S_3$. (**6**) IR: (KBr) cm-1: 3404 (NH), 1680 (C=N), 1354 (C–N), 1245 (S=O), 1140 (C–O–C), 1120 (C=S); ^{1}H NMR (DMSO-d_6) ppm: 4.62 (4H, s, $CH_2 \times 2$), 6.12 (2H, s, CH×2), 6.32 (furan, 6H), 6.61–8.0 (18H, m, Ar), 10.12 (2H, s, NH×2); Ana $C_{40}H_{32}N_6O_8S_3$.