

Note

Synthesis and evaluation of some novel substituted 1,3,4-oxadiazole and pyrazole derivatives for antitubercular activity

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A series of 1,3,4-oxadiazole and pyrazole derivatives have been synthesized and evaluated for antitubercular activity. All the structures of the newly synthesized compounds have been supported by IR, ¹H NMR, MS and CHN analysis. All the compounds have shown promising antitubercular activity when compared with the standard drug Streptomycin.

Keywords: 1,3,4-Oxadiazole, pyrazole, antitubercular, Mannich base

Tuberculosis is currently the leading killer of the youth, women and AIDS patients throughout the world. Although many active antitubercular agents have since been developed, a disturbing co-occurrence with the use of present drugs as single agent has developed drug resistance^{1,2}. The development of this resistance can be forestalled through the use of combination regimens, it is clear that drug resistance will continue to be a problem³. Therefore, there is a clear need for the discovery of new derivatives with antitubercular activity for the management of tuberculosis.

It was observed from the literature that certain five membered heterocyclic compounds possess interesting biological activity. Among them the compounds bearing 1,3,4-oxadiazole and pyrazole nucleus have wide applications in medicinal chemistry. These compounds also have been reported to have significant antitubercular activity^{4,5}.

Result and Discussion

Compounds were synthesized as per the **Scheme I**, where 2-mercaptop-1,3,4-oxadiazole derivatives by

reacting salicylic acid hydrazide with carbon disulfide followed by condensation reaction. 5-(Substituted aryl)-1,3,4-oxadiazole derivatives were synthesized by reacting salicylic acid hydrazide with aromatic acid. 3-Methyl-pyrazol-5(4H)-one derivatives were synthesized by reacting salicylic acid hydrazide with ethyl acetoacetate followed by Mannich reaction. The structures of the synthesized compounds were confirmed by IR, NMR, MS and CHN analysis (**Table I**).

All these compounds were screened for antitubercular activity by Middle Brook 7H9 agar medium against H₃₇Rv strain. Streptomycin was used as standard drug. Compounds **1a**, **2b**, **3a**, **3b**, **3c**, and **3e** have shown promising antitubercular activity. Compounds **1b**, **1c**, **3d** have shown moderate activity.

Methodology for anti-tubercular activity⁶

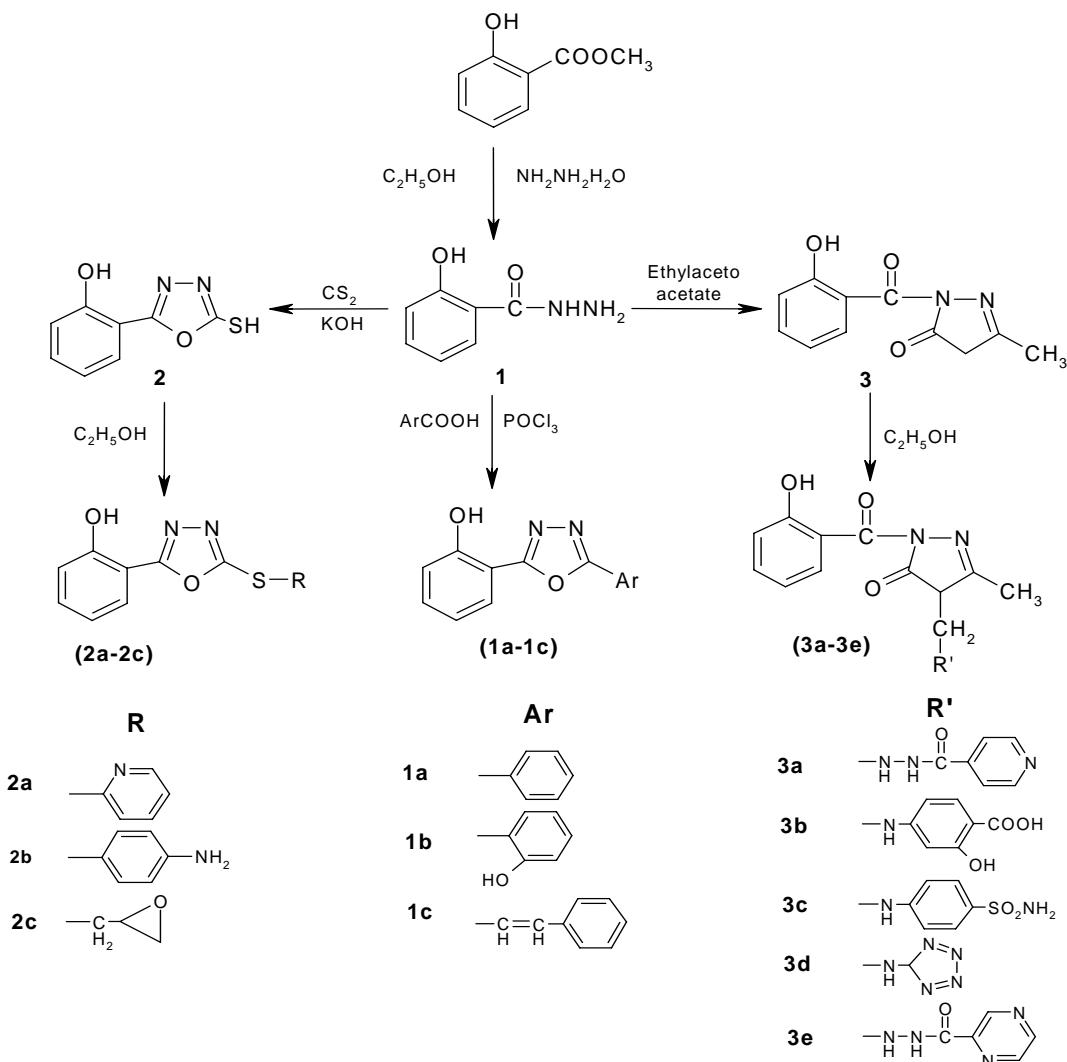
The antitubercular screening was carried out by Middle Brook 7H9 agar medium against H₃₇Rv strain. Middle Brook 7H9 agar medium containing different derivatives, standard drug as well as control, was inoculated with *Mycobacterium tuberculosis* H₃₇Rv strain. The inoculated bottles were incubated at 37°C for 4 weeks. At the end of 4 weeks they were checked for growth and scaled for inhibition.

Experimental Section

Melting points were determined using open capillary method and are uncorrected. The compounds were checked for homogeneity by TLC on silica gel G. The IR spectra were recorded on Thermo Nicolet IR 200 spectrophotometer using KBr disc method. The ¹H NMR spectra were recorded on sophisticated multinuclear FT-NMR spectrometer model Avance-II (Bruker) using DMSO-*d*₆ as solvent and TMS as internal standard.

Synthesis of 2-hydroxybenzohydrazide^{7,1}

A mixture of 0.1 mole (15.2 mL) methyl salicylate and 0.2 mole (10 mL) hydrazine hydrate were refluxed in 50 mL of 95% ethanol for 15 hr. The resultant mixture was concentrated, cooled and poured into crushed ice. The solid mass thus separated out was filtered, dried and purified by



Scheme I

recrystallization from ethanol. Yield 77%, m.p. 142–44°C; R_f value: 0.49.

Synthesis of 5-(2-hydroxyphenyl)-2-mercaptop-1,3,4-oxadiazole^{8,9}, 2

A mixture of 0.01 mole (1.52 g) of 2-hydroxybenzohydrazide **1**, 0.01 mole (0.56 g) of potassium hydroxide and 10 mL of carbon disulfide were refluxed in 50 mL of 95% ethanol for 12 hr. The resultant mixture was concentrated and cooled to RT. Then it was acidified with dil. HCl. The solid mass thus separated out was filtered, dried and purified by recrystallization from ethanol. Yield 63%, m.p. 186–88°C; R_f value: 0.56. IR (KBr): 3085.23(O-H str), 2890.30(Ar C-H str), 1629.08(C=N str) 1056.17(C-O-C str), 2736 cm^{-1} (C-SH); ^1H NMR (DMSO- d_6): δ 6.92–7.68(m, 8H, Ar. CH), 8.03(s, 1H, SH), 10.00(s, 1H, OH).

Synthesis of 5-(2-hydroxyphenyl)-2-(pyridinylthio)-1,3,4-oxadiazole, 1a

A mixture of 0.005 mole (0.97 g) of 5-(2-hydroxyphenyl)-2-mercaptop-1,3,4-oxadiazole **2** and 0.005 mole (0.5 g) of 2-chloropyridine were refluxed in 25 mL of 95% ethanol for 2 hr. The resultant solution was concentrated. The solid mass thus separated out was filtered, dried and purified by recrystallization from ethanol.

Synthesis of 1b and 1c

A mixture of 0.005 mole (0.97 g) of 5-(2-hydroxyphenyl)-2-mercaptop-1,3,4-oxadiazole **2** and 0.005 mole of *p*-chloroaniline **1b** / epichlorohydrine **1c** were refluxed in 25 mL of 95% ethanol for 2 hr. The resultant solution was concentrated. The solid mass thus separated out was filtered, dried and

Table I — Analytical and antitubercular activity data of the synthesized compounds **1a-3e**

Compd	Mol. Formula	Mol. Wt.	m.p. °C	Yield %	Calcd % (Found)			Antitubercular activity	
					C	H	N	50 µg/mL	100 µg/mL
1a	C ₁₃ H ₉ N ₃ O ₂ S	271	183-85	61	57.55 (57.37)	3.34 3.22	15.49 15.65)	S	S
1b	C ₁₄ H ₁₁ N ₃ O ₂ S	285	89-90	68	58.93	3.89	14.73	R	R
1c	C ₁₁ H ₁₀ N ₂ O ₃ S	250	197-99	67	52.79 (52.55)	4.03 4.21	11.19 11.28)	R	R
2a	C ₁₄ H ₁₀ N ₂ O ₂	238	136-38	73	70.58 (70.36)	4.23 4.32	11.76 11.65)	R	R
2b	C ₁₄ H ₁₀ N ₂ O ₃	254	90-92	55	66.14	3.96	11.02	S	S
2c	C ₁₆ H ₁₂ N ₂ O ₂	264	86-88	65	72.72	4.58	10.60	R	R
3a	C ₁₈ H ₁₇ N ₅ O ₄	367	124-26	78	58.85 (58.69)	4.66 4.45	19.06 19.17)	S	S
3b	C ₁₉ H ₁₇ N ₃ O ₆	383	315-17	80	59.53	4.47	10.96	S	S
3c	C ₁₈ H ₁₈ N ₄ O ₅	337	110-12	83	58.37 (58.40)	4.86 4.50	15.13 15.02)	S	S
3d	C ₁₃ H ₁₃ N ₇ O ₃	315	80-82	61	49.52	4.16	31.10	R	R
3e	C ₁₇ H ₁₆ N ₆ O ₄	368	87-89	59	55.43 (55.29)	4.38 4.52	22.82 22.67)	S	S

Streptomycin

S S

The combustion analysis of compounds synthesized is within the limits of permissible errors.

R - Resistant; S - Sensitive

Streptomycin was used as standard drug

purified by recrystallization from ethanol respectively.

Synthesis of 5-(2-hydroxyphenyl)-2-phenyl-1,3,4-oxadiazole^{8,9}, **2a**

A mixture of 0.01 mole (1.52 g) 2-hydroxybenzohydrazide **1** and 0.01 mole (1.22 g) of benzoic acid was dissolved in phosphorus oxychloride and refluxed for 18-22 hr. The reaction mixture was slowly poured over crushed ice and kept overnight. The solid mass thus separated out was filtered, dried, and purified by recrystallization from ethanol. The compounds **2b** and **2c** were synthesized following a similar procedure.

Synthesis of 1-(2-hydroxybenzoyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one⁷, **3**

A mixture of 0.01 mole (1.52 g) of 2-hydroxybenzohydrazide **1** and 0.1 mole (13 mL) of ethylacetacetate were heated on water bath for 2 hr with stirring from time to time with a glass rod. The resultant heavy reddish syrup was allowed to cool to RT. It was washed thoroughly with ether to remove coloured impurities. The solid thus separated out was filtered, dried and purified by recrystallization from

ethanol. Yield 75%, m.p. 118-20°C; R_f value: 0.63. IR (KBr): 3099.40 (O-H str), 3011.05 (Ar C-H str), 3396.02 (N-H str), 1614.87(C=N str) 1698.30 cm⁻¹ (C=O str).

Synthesis of N-((1-(2-hydroxybenzoyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl) methyl)isonicotinohydrazide, **3a**

A mixture of 0.005 mole (1.09 g) of 1-(2-hydroxybenzoyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one **3**, 5 mL of formaldehyde and 0.005 mole (0.68 g) of isonicotinic acid hydrazide was refluxed with 25 mL of 95% ethanol for 2 hr. The resultant mixture was concentrated. The resultant solid mass was dried and purified by recrystallization from ethanol. The compounds **3b-e** were synthesized following a similar procedure.

Spectral characterization data

1a: IR (KBr): 3196.08(O-H str), 2970.70(Ar C-H str), 1611.04(C=N str) 1041.47(C-O-C str), 688.01 cm⁻¹ (C-S-C str); ¹H NMR (DMSO-*d*₆): δ 6.96-7.73(m, 8H, Ar. CH), 9.25(s, 1H, OH).

1b: IR (KBr): 3157.08(O-H str), 3040.70 (Ar C-H str), 3397.08(N-H str), 1621.39 (C=N str) 1057.68 (C-O-C str), 688.01 cm⁻¹ (C-S-C str); MS: *m/z* 285 [M⁺].

1c: IR (KBr): 3198.91 (O-H str), 2975.11 (Ar C-H str), 1611.33 (C=N str) 1042.13 (C-O-C str), 687.50 cm⁻¹ (C-S-C str).

2a: IR (KBr): 3201.40 (O-H str), 3059.90 (Ar C-H str), 1623.70 (C=N str) 1069.10 cm⁻¹ (C-O-C str).

2b: IR (KBr): 3070.69 (O-H str), 2923.94 (Ar C-H str), 1613.52 (C=N str) 1005.83 cm⁻¹ (C-O-C str); ¹H NMR (DMSO-*d*₆): δ 6.96-7.71 (m, 8H, Ar. CH), 10.45 (s, 1H, OH).

2c: IR (KBr): 3058.90 (O-H str), 2927.10 (Ar C-H str), 1632.30 (C=N str) 1080.80 cm⁻¹ (C-O-C str).

3a: IR (KBr): 3213.02 (O-H str), 3035.35 (Ar C-H str), 3362.55(N-H str), 1600.32 (C=N str) 1660.70 cm⁻¹ (C=O str); ¹H NMR (DMSO-*d*₆): δ 6.78-8.78 (m, 8H, Ar. CH), 10.55 (s, 1H, OH), 5.76(s, 1H, NH), 7.96(s, 1H, CONH), 2.47(s, 3H, CH₃), 2.36-2.37(s, 2H, CH₂), 2.30(s, 1H, CH); MS: *m/z* 367 [M⁺].

3b: IR (KBr): 3205.40 (O-H str), 3062.00 (Ar C-H str), 3425.80 (N-H str), 1608.60 (C=N str) 1697.90 cm⁻¹ (C=O str).

3c: IR (KBr): 3160.50 (O-H str), 3078.50 (Ar C-H str), 3382.40 (N-H str), 1645.80 (C=N str) 1716.70 cm⁻¹ (C=O str).

3d: IR (KBr): 3208.33 (O-H str), 3048.19 (Ar C-H str), 3453.21 (N-H str), 1611.33 (C=N str) 1687.91 cm⁻¹ (C=O str)

3e: IR (KBr): 3162.12 (O-H str), 2924.80 (Ar C-H str), 3387.55(N-H str), 1600.71 (C=N str) 1682.98 cm⁻¹ (C=O str); ¹H NMR (DMSO-*d*₆): δ 6.97-8.86 (m, 8H, Ar. CH), 10.39 (s, 1H, OH), 5.23(s, 1H, NH), 7.76(s, 1H, CONH), 2.50(s, 3H, CH₃), 2.39-2.41(s, 2H, CH₂), 2.28(s, 1H, CH).

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