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Synthesis and evaluation of phenoxy acetic acid derivatives as a anti-mycobacterial agents

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Abstract—In present investigation, 2-(4-formyl-2-methoxyphenoxy) acetic acid on condensation with various ketones in methanolic KOH solution yielded the corresponding chalcones (**1–3**). These corresponding chalcones were reacted with appropriate acid hydrazide in glacial acetic acid led to the formation of phenoxy acetic acid derivatives. All newly synthesized compounds were evaluated for their anti-mycobacterial activities against *Mycobacterium tuberculosis* $H_{37}Rv$.

Tuberculosis is by far the most frequently encountered mycobacterial disease in the world. 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. The emergence of AIDS, decline of socioeconomic standards and a reduced emphasis on tuberculosis control programs contribute to the disease's resurgence in industrialized countries. Resistance of *Mycobacterium tuberculosis* strains to anti-mycobacterial agents is an increasing problem worldwide. However, powerful new anti-TB drugs with new mechanism of action have not been developed in the last forty years. In spite of severe toxicity on repeated dosing of isoniazid (INH), it still considered to be a first line drug for chemotherapy of tuberculosis. Literature survey reveals pyrazoline derivative possess the various biological activities viz. anti-bacterial and anti-fungal,[1] anti-diabetic,[2] anti-inflammatory [3] and also active against many Mycobacterias.[4–7] The current work describes the synthesis of novel pyrazoline moiety with encouraging anti-mycobacterial activity against *M. tuberculosis* $H_{37}Rv$ and INH resistant *M. tuberculosis* (INHR-MTB) (Scheme 1).

The synthesis of pyrazoline derivatives has been carried out following the steps shown in schemes. In the initial step, chalcones (**1–3**) were synthesized by condensing 2-(4-formyl-2-methoxyphenoxy) acetic acid with various ketones in dilute methanolic potassium hydroxide solution at room temperature by Claisen–Schimidt condensation. The compounds (**4–24**) were synthesized by reacting chalcones with appropriate aryl acidhydrazides in glacial acetic acid at 4 h. The purity of the compounds was checked by single spot TLC method using various mobile bases; Spectral data (IR, ^{1}H NMR, ^{13}C NMR, and Mass). Both analytical and spectral data of all the newly synthesized compounds were in full agreement with purposed structures (Table 1).

Twenty compounds were screened for their anti-mycobacterial activity against *M. tuberculosis* H_{37} Rv using BACTEC-460 radiometric system[8,9] and INH resistant *M. tuberculosis* (INHR-MTB) using agar dilution method.[10] Among the chalcones (**1–3**) and pyrazolines (**4–24**). Compounds **7** and **10** produced highest efficacy and exhibited >99% inhibition at ~6.25 μg/ml. Compounds **14** exhibited ~95 % inhibition against *M. tuberculosis* at MIC ~6.25 μg/ml in the primary screen Table 2. The MIC was defined as the minimum concentration of compound required to inhibit 90% of bacterial growth and MICs of the compounds were reported in Table 2 with standard drug INH for comparison. Among the twenty newly synthesized compounds three compounds were found to be most active compounds with minimum inhibitory

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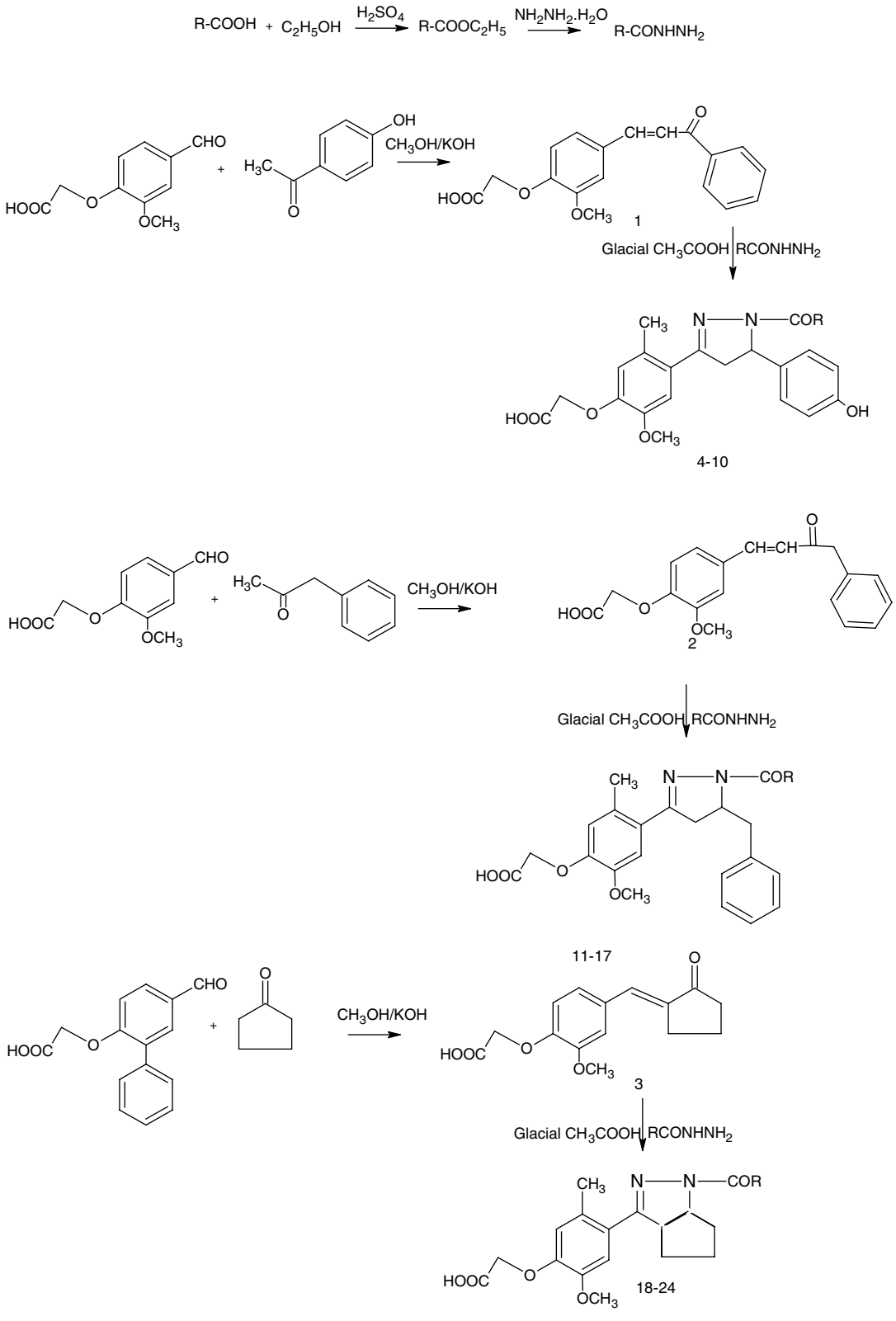

Scheme 1. Protocol for the synthesis of phenoxy acetic acid derivatives.

concentration of less than 1 μg/ml. Rest of the compounds shows low to moderate activity. These anti-mycobacterial data clearly show that the presence 4-hydroxy phenyl substitution 5th position with β-napthox and phenoxy substitution at pyrazoline causes remarkable improvement in anti-tubercular activity

Table 1. Physical constants of the synthesized compounds

Compound	R^1	M.wt	M.F	R_f	Mp	% yield
4	C_6H_5	446.45	$C_{25}H_{22}N_2O_6$	0.95	122	72
5	4-NO_2—C_6H_4	491.45	$C_{25}H_{21}N_3O_8$	0.90	168	75
6	C_6H_5—NH—C_6H_4	537.56	$C_{31}H_{27}N_3O_6$	0.81	114	69
7	β-$C_{10}H_7$—O—CH_2	526.53	$C_{30}H_{26}N_2O_7$	0.73	138	90
8	α-$C_{10}H_7$—O—CH_2	526.53	$C_{30}H_{26}N_2O_7$	0.76	119	85
9	$C_6H_5CH_2$	460.47	$C_{26}H_{24}N_2O_6$	0.83	94	65
10	$C_6H_5OCH_2$	476.47	$C_{26}H_{24}N_2O_7$	0.75	120	76
11	C_6H_5	445.49	$C_{26}H_{25}N_2O_5$	0.65	126	80
12	4-NO_2—C_6H_4	490.48	$C_{26}H_{24}N_3O_7$	0.95	134	90
13	C_6H_5—NH—C_6H_4	536.60	$C_{32}H_{30}N_3O_5$	0.93	106	76
14	β-$C_{10}H_7$—O—CH_2	525.57	$C_{31}H_{29}N_2O_6$	0.72	142	68
15	α-$C_{10}H_7$—O—CH_2	525.57	$C_{31}H_{29}N_2O_6$	0.74	104	75
16	$C_6H_5CH_2$	459.51	$C_{27}H_{27}N_2O_5$	0.77	110	77
17	$C_6H_5OCH_2$	475.51	$C_{27}H_{27}N_2O_6$	0.85	128	67
18	C_6H_5	395.43	$C_{22}H_{23}N_2O_5$	0.73	95	90
19	4-NO_2—C_6H_4	404.42	$C_{22}H_{22}N_3O_7$	0.80	104	82
20	C_6H_5—NH—C_6H_4	486.54	$C_{28}H_{28}N_3O_5$	0.82	72	65
21	β-$C_{10}H_7$—O—CH_2	475.51	$C_{27}H_{27}N_2O_6$	0.84	96	76
22	α-$C_{10}H_7$—O—CH_2	475.51	$C_{27}H_{27}N_2O_6$	0.70	138	74
23	$C_6H_5CH_2$	409.45	$C_{23}H_{25}N_2O_5$	0.79	144	88
24	$C_6H_5OCH_2$	425.45	$C_{23}H_{25}N_2O_6$	0.81	160	70

Recrystallization: ethanol, petroleum ether.

Table 2. Anti-mycobacterial activity of the synthesized compounds

Compound	R^1	Inhibition (primary screen) (%)		Primary screen (6.25 μg/ml)		(MIC) μg/ml	
		MTB[a]	MTB[b]	MTB[a]	MTB[b]	MTB[a]	MTB[b]
4	C_6H_5	72	72	>6.25	>6.25	>6.25	>6.25
5	4-NO_2—C_6H_4	74	70	>6.25	>6.25	6.25	6.25
6	C_6H_5—NH—C_6H_4	62	54	>6.25	>6.25	>6.25	>6.25
7	β-$C_{10}H_7$—O—CH_2	99	99	6.25	6.25	0.10	0.70
8	α-$C_{10}H_7$—O—CH_2	61	58	>6.25	>6.25	>6.25	>6.25
9	$C_6H_5CH_2$	28	22	>6.25	>6.25	>6.25	>6.25
10	$C_6H_5OCH_2$	99	99	6.25	6.25	0.10	0.64
11	C_6H_5	12	18	>6.25	>6.25	>6.25	>6.25
12	4-NO_2—C_6H_4	64	50	>6.25	>6.25	>6.25	>6.25
13	C_6H_5—NH—C_6H_4	08	18	>6.25	>6.25	>6.25	>6.25
14	β-$C_{10}H_7$—O—CH_2	95	90	6.25	6.25	0.22	0.94
15	α-$C_{10}H_7$—O—CH_2	18	20	>6.25	>6.25	>6.25	>6.25
16	$C_6H_5CH_2$	34	34	>6.25	>6.25	>6.25	>6.25
17	$C_6H_5OCH_2$	94	92	6.25	6.25	>6.25	>6.25
18	C_6H_5	24	42	>6.25	>6.25	>6.25	>6.25
19	4-NO_2—C_6H_4	26	30	>6.25	>6.25	>6.25	>6.25
20	C_6H_5—NH—C_6H_4	21	24	>6.25	>6.25	>6.25	>6.25
21	β-$C_{10}H_7$—O—CH_2	91	94	>6.25	>6.25	6.12	6.25
22	α-$C_{10}H_7$—O—CH_2	54	50	>6.25	>6.25	>6.25	>6.25
23	$C_6H_5CH_2$	21	24	>6.25	>6.25	>6.25	>6.25
24	$C_6H_5OCH_2$	87	85	>6.25	>6.25	>6.25	>6.25
INH	—	96	90	6.25	6.25	0.10	1.56

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

against both *M. tuberculosis* H_{37} Rv and INH resistant *M. tuberculosis*.

To summarize, we have synthesized new class of phenoxy acetic acid derivatives as a novel class of anti-tubercular agents. The newly synthesized novel heterocyles exhibited promising anti-tubercular activities against both drug-sensitive & drug-resistant strains of *M. tuberculosis*. Among the compounds **7** and **10** was equally active as INH against *M. tuberculosis* H_{37} Rv and more than two times potent than INH against INH resistant *M. tuberculosis*. These results make novel phenoxy acetic derivatives 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 anti-mycobacterial 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.2006.06.021.

References and notes

1. Soliman, R.; Habib, N. S.; Ashour, F. A.; El-Taiebi, M. *Boll Chim. Farm* **2001**, *140*, 140.
2. Ahn, J. H.; Kim, H. M.; Jung, S. H.; Kang, S. K.; Kim, K. R.; Rhee, S. D.; Yang, S. D.; Cheon, H. G.; Kim, S. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4461.
3. Nasr, M. N.; Said, S. A. *Arch. Pharm. (Weinheim)* **2003**, *336*, 551.
4. Kucukguzel, S. G.; Rollas, S. *Farmaco* **2002**, *57*, 583.
5. Guniz Kucukguzel, S.; Rollas, S.; Erdeniz, H.; Kiraz, M.; Cevdet Ekinci, A.; Vidin, A. *Eur. J. Med. Chem.* **2000**, *35*, 761.
6. Nauduri, D.; Reddy, G. B. *Chem. Pharm. Bull. (Tokyo)* **1998**, *46*, 1254.
7. Santilli, A. A.; Kim, D. H.; Gregory, F. J. *J. Pharm. Sci.* **1975**, *64*, 1057.
8. Interleid, B. Antibiotic in laboratory medicine. In lorian, V., Ed., 3rd Ed.; Williams and Wikins: Baltimore, 1991; p p. 134.
9. Colins, L.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **1997**, *41*, 1004.
10. Heifets, L. B.; Flory, M. A.; Lindholm-Levy, P. J. *Antimicrob. Agents Chemother.* **1989**, *33*, 1252.