ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in
S.R.Pattan et al /J. Pharm. Sci. & Res. Vol.1(3), 2009,63-68

Synthesis and Evaluation of Some New Pyrazolo Phenoxy Acetic Acid Derivatves For Their Antitubercular Activity

S.R.Pattan*[1] R.L.Hullolikar, J. S.Pattan[2] , B.P.Kapadnis[3],N.S. Dighe[1] ,S.S.Dengale[1], Ana Nikalje, S.A.Nirmal[1]

1. Department of Medicinal Chemistry, Pravara Rural College Of Pharmacy, Pravaranagar, Maharashtra,India
2. Department of Microbiology, PVP Science College, Pravaranagar,M.S.India
3. Department of Microbiology, University of Pune, Pune,M.S. India

ABSTRACT

The present research work is aimed to synthesize some novel substituted pyrazolo phenoxy acetic acid. The ten new derivatives of phenoxy acetic acid (Scheme) were synthesized during the course of research work. The structures of compounds have been established by means of FT IR, ^{1}H-NMR and elemental analysis. All the compounds were evaluated for anti-tubercular activity Middle brook 7H9 agar medium against H_{37}Rv Strain.Out of ten compounds **P_1, P_2,P_6, P_7, P8, P_{10}** shown maximum anti-tubercular activity.

Key-words: Anti-tubercular, Chalcones, Mannich reaction, Pyrazolo phenoxy acetic acid derivatives.

INTRODUCTION

Tuberculosis (abbreviated as TB for Tubercle Bacillus) is a common and deadly infectious disease that is caused by mycobacterium, primarily TB. Tuberculosis most commonly affects the lungs (as pulmonary TB) but can also affect the central nervous system, the lymphatic system, the circulatory system, the urinogenital, bones, joints and even the skin. Other mycobacteria such as *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium canetti* and *Mycobacterium microti* can also cause tuberculosis, but these species do not usually infect healthy adults. [1]

As MTB only has one phospholipids outer membrane, it is classified as Gram-positive bacteria. However, if a Gram stain is performed, MTB either stains very weakly Gram-positive, or does not retain dye, due to the high lipid content of its cell wall. Normally, the bacteria can only grow within a host organism, so *in vitro* culture of *M. tuberculosis* took a long time to develop, but is now a routine laboratory procedure. The *M. tuberculosis* complex includes 3 other mycobacteria which can cause tuberculosis: *M. bovis*, *M. africanum* and *M. microti* the first two are very rare causes of disease in immunocompetent people and *M. microti* is not usually pathogenic, although it is possible that the prevalence of *M. microti* infections has been underestimated. Other pathogenic mycobacteria are known, such as *Mycobacterium leprae*, *Mycobacterium avium* and *M. kansasii*. The last two are part of the group defined as Nontuberculous mycobacteria (NTM). Nontuberculous mycobacteria are mycobacteria that are not part of the *M. tuberculosis* complex and do not cause leprosy but do cause pulmonary diseases resembling tuberculosis.

The increasing prevalence of multidrug-resistant (MDR)-TB has greatly contributed to the increased difficulties in the control of TB. Because of the

***For Correspondence:**
shashipattan@yahoo.com,nachiket1111@rediffmail.com
Telephone-+91-2422-273528
Fax-+91-2422-273528

global health problems of TB, the increasing rate of MDR-TB and the high rate of a co-infection with HIV, the development of potent new anti-TB drugs without cross-resistance with known antimycobacterial agents are urgently needed.

MATERIAL AND METHODS

Synthesis of 4-formyl phenoxy acetic acid [3] (I):

To a mixture of 1.0gm of the p-hydroxy benzaldehyde and 3.5ml of 33% of NaOH solution in a beaker, add 2.5ml of 50% chloroacetic acid solution. Add a little water to dissolve the solution the sodium salt of the phenol and heated gently on boiling water bath for one hour. After cooling dilute with 10 ml of water, acidify to congo red with hydrochloric acid and extract with 30 ml of ether wash the ethereal extract with 10mL of water and extract the aryloxyacetic acid by shaking with 25 ml of 5% sodium carbonate solution. Acidify the sodium carbonate extract with dilute hydochoric acid collect the 4-formyl phenoxy acetic acid which separates and recrystallized with ethanol. Melting point was 132^{o}C.

Synthesis of chalcone derivatives from 4-formyl phenoxy acetic acid [4,5] (II):

A mixture of 4-formyl phenoxy acetic acid (0.01mole) and aryl aldehyde (0.01 moles) was stirred in ethanol (30 ml) and then an aqueous solution of KOH (40%, 15 ml) added to it. The mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with HCl. The solid separated was filtered and crystallized from ethanol. Melting point observed 145-155^{o} C.

Synthesis of 2 -(4-(5-substituted phenyl-4*H*-pyrazol-3-yl) phenoxy) acetic acid [6] (III):

A mixture of chalcone derivative (0.01mole) and hydrazine hydrate (0.02mole) in 20 ml of ethanol and 2-3 drops of glacial acetic acid and was refluxed for 8 hours the resulting solution was left overnight in a refrigerator the product was filtered and recrystallized from ethanol yield of the product 65-75%.

Synthesis of 2-(4-(4-((2-Substituted) methyl)-5-Substituted phenyl- 4*H*-pyrazol-3-yl) phenoxy) ac etic a cid[5] (P_1-P_{10}):

0.01 mole of 2-(4-(5-substituted phenyl-4*H*-pyrazol-3-yl) phenoxy) acetic acid (III) and 0.01mole of secondary amine was dissolved in ethanol to above mixture 0.01 mole of formaldehyde was added and refluxed for 2 hour the reaction mixture was cooled and poured over crushed ice and kept in refrigerator for over night the product was filtered dried and recrystallized, the melting point and percentage (%) yields were reported in the Table no 2.

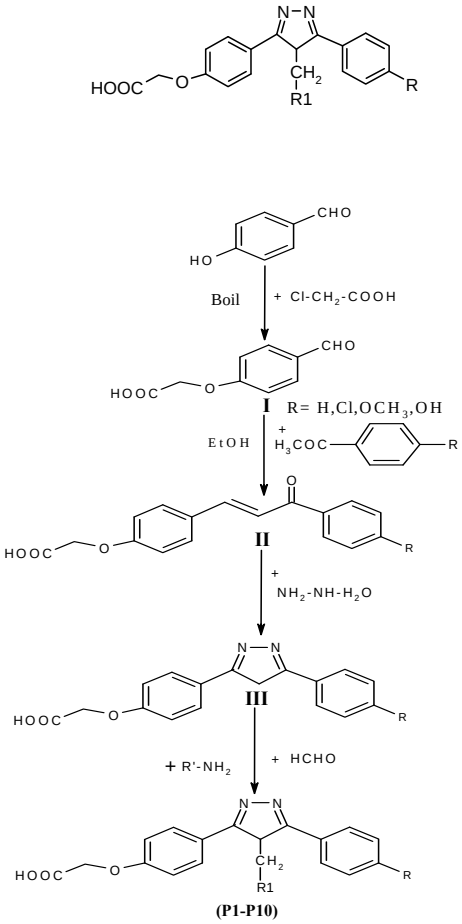
ANTI-TUBERCULAR ACTIVITY [2]

The antitubercular screening was carried out by Middle brook 7H9 agar medium against H_{37}Rv. Strain. Middle brook 7H9 agar medium containing different derivatives, standard drug as well as control, Middle brook 7H9 agar medium was inoculated with *Mycobacterium tuberculosis* of H_{37}Rv Strain. The inoculated bottles were incubated for 37°C for 4 weeks. At the end of 4 weeks they were checked for growth.

RESULT AND DISCUSSION

Around 10 substituted Pyrazoles were synthesized by reacting p-hydroxy

SCHEME- (P_1-P_{10}):



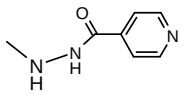
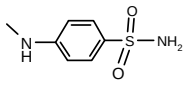
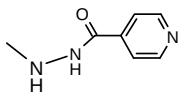
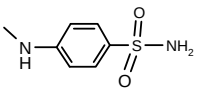
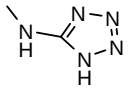
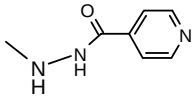
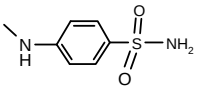
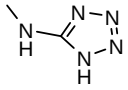
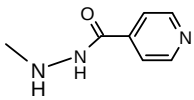
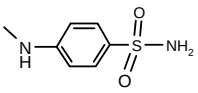
COMPOUNDS	R	R_1
P_1	H	
P_2	H	
P_3	Cl	
P_4	Cl	
P_5	Cl	
P_6	OCH_3	
P_7	OCH_3	
P_8	OCH_3	
P_9	OH	
P_{10}	OH	

Table No-2: Analytical & Physicochemical data of the synthesized compounds (P_1-P_{10})

Comp.	Mol. Formula	Mol. Wt.	m.p. ° C	Yield %	Elemental analyses Calcd. (Found)			LogP	CLogP	CMR
					C	H	N			
P_1	$C_{24}H_{21}N_5O_4$	443.45	124-28	61	65.95 (65.00)	4.98 (4.77)	15.92 (15.79)	1.6	2.39	12.67
P_2	$C_{24}H_{22}N_4O_5S$	478.52	137-42	68	60.25	4.63	11.71	2.78	2.86	13.25
P_3	$C_{24}H_{20}ClN_5O_4$	477.90	114-18	67	60.32	4.22	14.65	2.22	3.10	13.16
P_4	$C_{24}H_{21}ClN_4O_5S$	512.97	171-175	73	56.40 (56.19)	4.25 (4.13)	11.10 (10.92)	3.34	3.57	13.75
P_5	$C_{19}H_{16}ClN_7O_3$	425.83	154-59	55	53.85	3.95	23.20	3.04	2.42	11.30
P_6	$C_{25}H_{23}N_5O_5$	473.48	120-124	65	63.42	4.90	14.79	1.73	2.31	13.29
P_7	$C_{25}H_{24}N_4O_6S$	508.55	144-48	78	59.25 (59.04)	4.85 (4.76)	11.20 (11.02)	2.65	2.77	13.87
P_8	$C_{20}H_{19}N_7O_4$	421.41	105-08	80	57.00	4.54	23.27	2.35	1.63	11.43
P_9	$C_{24}H_{21}N_5O_5$	459.45	164-167	83	63.12 (62.74)	4.82 (4.61)	15.46 (15.24)	1.21	1.75	12.82
P_{10}	$C_{24}H_{22}N_4O_6S$	494.52	88-92	53	58.30	4.48	11.35	2.29	1.91	13.75

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

Table No-3: Infra Red / ^{1}H NMR spectral data of the synthesized compounds (P_1-P_{10})

Compd. Code	IR Bands (cm^{-1})	Types of Vibrations	δ Values in ppm	No. Of Protons
P_1	2854,2972 3045,1513 2927,1605 763,838 3214	O-H Str.-C-H Ar. Str.-C=N Str. -C-H def.-C=O str.C-H def.-N-H str.	11.82,1.25 9.78,2.49 3.47-3.56 2.58-2.49 8.7-7.59	1H of –COOH 1H of Pyrazole 1H of 2^O NH 1H of Amine 2H of -CH_2 2H of CH_2 sub.to pyrazole 12H of Ar & Pyridine
P_2	2858,2967 2952,3249 1510,1594	-O-H Str.-C-H Ar.Str.-N-H Str. -C=N Str.-C=O Str.		
P_3	2852,3073 1513,3219 1591,2923 832	-O-H Str.-C-H Ar.Str.-C=N Str. -N-H Str.-C=O str. -C-H Alk.str.-C-Cl str.		
P_4	2853,2924 1512,1596 829,1151 3247	-O-H Str.-C-H Ar.Str.-C=N Str. -C=O Str.-C-Cl str.-S=O str.-N-H str.	10.92,7.39 8.8,7.12-8.10 1.7,3.23,3.49	1H of –COOH 2H of -SO_2NH_2 1H of Ar.-C-NH 12H of Ar.CH 1H of Pyrazole 2H of –CH_2sub. Pyrazole 2H of -CH_2
P_5	2852,2922 1513,1590 831	-O-H Str.-C-H Ar.Str.C=N Str. -C=O Str.-C-Cl str.		
P_6	2851,2922 1513,1176 3067,1605 836	-O-H Str.-C-H Ar.Str.-C=N Str. -C-O- Str.-N-H str.-C=O str. -C-H def.		
P7	2849,3068 3264,1599 1513,832 2926,1152	-O-H Str.-C-H Ar. Str.-N-H Str. -C=O Str.-C=N Str.-C-H def. -C-H str.-S=O str.	7.08-8.10 12.34,9.7 1.7.3.22 3.49.3.83	12H of Ar. CH 1H of -COOH 1H of Ar-C-NH 1H of Pyrazole 2H of CH2 2H of CH2 sub. to -COOH 1H of –OCH3
P8	2851,2922 3068.1604 1511	O-H Str. -C-H Ar.Str.-N-H Str.-C=O Str.-C=N Str.		
P9	3225.2924 3045.1585 1516.2860	-Ar-O-H Str.-C-H Ar.Str.-N-H Str. -C=O Str.C=N Str. -O-H str.		
P10	3225.2924 3045.1599 1513.2860	-Ar-O-H Str.-C-H Ar.Str.-N-H Str. -C=O Str.-C=N Str.-O-H str.		

benzaldehyde reacted with chloroacetic acid and further treated with substituted acetophenones to get chalcones (II).These chalcones were treated with hydrazine hydrate to get Pyrazoles. The Pyrazoles were treated with substituted amino compounds by Mannich reaction, using formalin. The structures of compounds have been established by means of FT IR, ^{1}H-NMR and elemental analysis. The synthesized compounds are subjected to antitubercular activities by Middle brook method using $H_{37}Rv$ Strain.

Compounds **P_1, P_2, P 6**, **P_7**, **P8,** and **P_{10}** have shown promising anti-tubercular activity against streptomycin as a standard drug.

ACKNOWLEDGEMENTS

Authors wish to thank Honorable Shri.Radhakrishna Vikhe Patil, Minister for Education, Law and Justice Govt. of Maharashtra for his constant encouragement and support. Our sincere thanks to Maj. Gen. U. M. Maindarkar, Director General Pravara Rural Education Society, Loni for providing all the facilities necessary for research work.

REFERENCES

[1] Hardman JG, Limbird LE. *Goodman Gilman's The Pharmacological Basis of Therapeutics*. 10th edition, New York: McGraw-Hill Medical Publishing Division; 2001: 687-730.

[2] Rang HP, Dale MM, Ritter JM, Moore P K. *Pharmacology. 5th Edition*, New Delhi: Elservier India Pvt Ltd; 2003: 667-72.

[3] Furniss BS, Hannaford AJ, Smith PWG, Patchel AR. *Vogel's Textbook of Practical Organic Chemistry. 5th edition*, Singapore, Published by Pearson education (Singapore) Pvt. Ltd. 1996, 1034,1050-53

[4] Bhat A.R,Chetan B.P and Srinivas M.T., *Indian Journal of Heterocyclic Chemistry*.2004;*13*:225-228

[5] Koneman EW, Allen SD, Janda MW, Washington CW. *Text book of Diagnostic Microbiology. 5th Edition*, Philadelphia: J B Lippincott company (P) Ltd; 1997; 935-939

[6] Salvemini D, Manning PJ, Zweifel BS, Seibert K, Conner J, Carrie MG, et al. *J Clin Invest* 1995; *96*:301-8.