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SYNTHESIS, CHARACTERIZATION AND ANTITUBERCULAR ACTIVITY OF 6-(ARYL)-2-(SUBSTITUTED METHYL)-4,5-DIHYDRO(*2H*)PYRIDAZIN-3-ONE DERIVATIVES AGAINST *MYCOBACTERIUM TUBERCULOSIS* H_{37}RV

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Keywords:

Pyridazinone, Antitubercular, Mycobacterium, Biological activities, Heterocyclic, synthesis

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ABSTRACT: Two series of pyridazinone derivatives, 6-(aryl)-2-(substituted methyl)-4,5-dihydro (*2H*) pyridazin-3-one derivatives (3a-8a and 3b-8b) were synthesized by reacting 6-phenyl substituted 2,3,4,5-Tetrahydro pyridazin-3-one (2a and 2b) with cyclic secondary amine under Mannich reaction conditions. These final compounds (3a-8a and 3b-8b) were characterized by spectral analysis (IR, ^{1}HNMR and mass spectroscopy) and evaluated for anti-tubercular activities against *Mycobacterium tuberculosis* H37Rv strain by Microplate Alamar Blue assay (MABA) method. Most of the compounds were showed significant anti-tubercular activity. Compounds (7a and 7b) were showed maximum antitubercular activity with 6.25 µg/ml minimum inhibitory concentration (MIC) value and compounds (4a, 5a, 8a and 3b, 4b, 6b, 8b) were exhibited 12.5 µg/ml MIC value and other remaining compounds (3a, 6a and 5a) were found less potent (12.5 µg/ml) MIC value than the reference drugs when compared with reference drugs [pyrizinamide (3.125 µg/ml)] and (streptomycin 6.25 µg/ml) MIC values. Among the synthesized pyridazinone derivatives, compound (7a and 7b) emerged as a lead compound with good anti-tubercular activity. These biological activities differences mainly depend on the different type of substitutions on the pyridazinone ring system.

INTRODUCTION: On the basis of literature report, nitrogen-containing heterocyclic compounds showed diverse pharmacological activities. In this series, pyridazinone derivatives were reported to exhibit diverse pharmacological activities. During recent years substituted pyridazinones have been a subject of demanding research due to their wide range of pharmacological actions [1-3].

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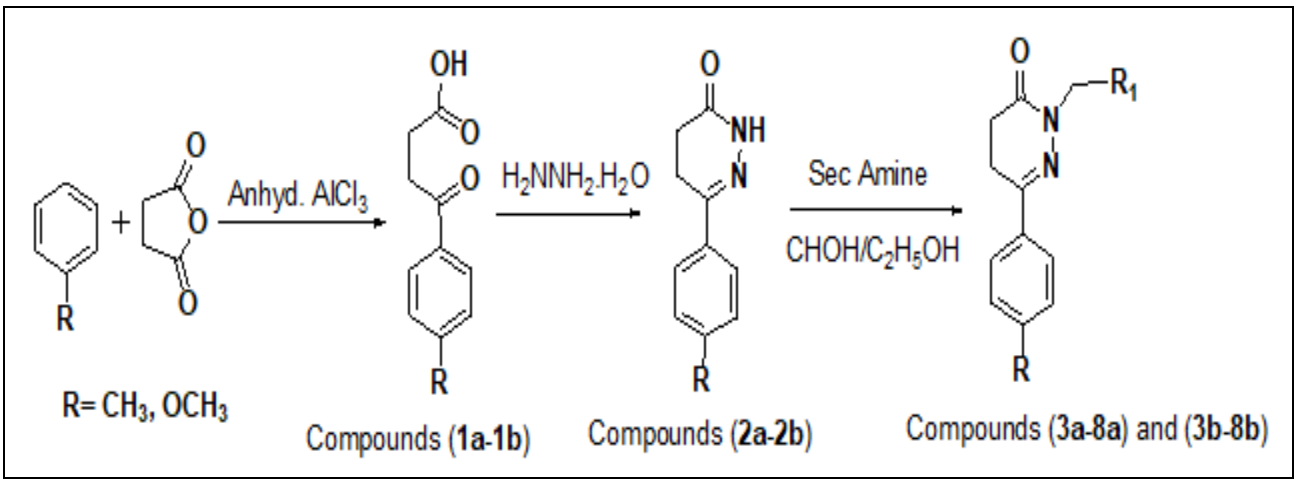
Differently substituted pyridazinone derivatives were exhibited diverse potential pharmacological activities like an antidepressant, antihypertensive, anti-thrombotic, anticonvulsant, cardiotonic, analgesic, anti-inflammatory, diuretics, antibacterial, anti-fungal, antiviral, anticancer, hypotensive, antiulcer and other biological activities [4-10].

Several pyridazinone derivatives like levosimendan, indolidan, bemoradan, pimobendan, emorfazone, minaprine, and azanrinone, *etc*. are used clinically for the treatment of various illnesses. Pyridazinones also has considerable interest in the preparation of organic agrochemicals [11-15].

Tuberculosis (TB) is an infectious disease and caused by mainly *Mycobacterium tuberculosis* (*M. tuberculosis*) strains. TB is a leading cause of death worldwide, mainly in developing countries. About one-third of the population is infected with TB with around 8 million new cases of TB occur per year. TB occurrence is also rising due to high HIV infection rates; both diseases growth at faster rates in co-infected persons. The resistance of *M. tuberculosis* strains to anti-TB drugs is arising problem. However, few potent new anti-TB drugs with new mechanism of action have been developed in the last some decades. Now efforts toward the development of novel anti-TB drugs, which are structurally dissimilar from currently used anti-TB drugs. The current work describes the synthesis of new pyridazinone derivatives with encouraging anti-TB activity [16-20].

It was observed that various pyridazinone derivatives possess antitubercular. In continuation of the work on pyridazinone derivatives, we have synthesized some pyridazinone derivatives and evaluated them for anti-TB activity against *M. tuberculosis* H37Rv strain by Microplate Alamar Blue Assay (MABA) method. The Friedel Craft acylation of aromatic hydrocarbon with succinic anhydride gave the β-aroyl propionicacids (1a-1b) in presence of aluminium chloride ($AlCl_3$). Compounds (1a-1b) on hydrazinolysis gave the 6-arylpyridazinones (2a-2b). The compounds (2a-2b) were reacted with cyclic secondary amine and formaldehyde to give the title compounds (3a-8a and 3b-8b) by Mannich reaction as shown in **Scheme 1**.

Methodology: Melting points (M.P) were determined by the open tube capillary method and were uncorrected. The purity of the compounds was checked by thin-layer chromatography (TLC) plates (silica gel G) which were visualized by exposing to iodine vapors and UV light. Elementary analyses were performed on a LECO CHNS 932 analyzer for C, H, N values agent and analyses for C, H, N were within ±0.4% of the theoretical values. The FT-IR spectra were recorded on Bio-rad FTS-135 spectrophotometer using potassium bromide (KBr) pellets; λmax values are given in cm^{-1}. The ^{1}HNMR spectra were recorded on Bruker Spectrospin DPX 300 MHz using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) scale. The FAB mass spectra were obtained on JEOL-JMSDX 303 system, equipped with direct inlet probe system.



SCHEME 1: SYNTHESIS OF 6-(ARYL)-2-(SUBSTITUTEDMETHYL)-4,5-DIHYDROPYRIDAZIN-3(*2H*)-ONE DERIVATIVES

Experimental Protocols:

Synthesis of Substituted β-aroylpropionic acids (1a and 1b): Take aluminum chloride (0.15 mol) in toluene or anisole (50 mL) in under anhydrous conditions, the mixture was refluxed on a water bath. Added succinic anhydride (0.10 mol) to the reaction mixture in small portions with nonstop stirring for 6 h. Then the reaction mixture was left overnight and acidic with ice-cold hydrochloric acid (2.5% v/v) solution. The separated precipitate was obtained and filtered it. It was purified by dissolving in 5% w/v sodium bicarbonate solution, followed by extraction with chloroform. The aqueous layer on acidification with dilute hydrochloric acid gave aroyl propionic acid (1a and 1b) and crystallized with aqueous ethanol [18-20].

Synthesis of 6-Substituted aryl-4,5-Dihydro-pyridazin-3-one (2a and 2b): To a solution of compound (1a or 1b) (0.1 mol) in methanol (30 mL), hydrazine hydrate (1 mL) and sodium acetate (0.5 g) were added and the mixture was refluxed for 6 h. The content was poured into cold water. The solid product was separated out and recrystallized with methanol [18-20].

General procedure for the synthesis of 6-(aryl)-2-(substituted methyl)-4, 5-dihydro-pyridazin-3(2H)-one (3a-8a and 3b-8b): To a solution of compounds (2a and 2b) (0.001 mol) in ethanol (30 ml), formaldehyde (38-42%) (1.5 ml) and cyclic secondary amine (0.001 mol) were added and the reaction mixture was refluxed for 18 hrs. After that the ethanol was distilled off and the residue was poured into crushed ice and kept overnight in refrigerator to separate out the compounds (3a-8a and 3b-8b), filtered it and recrystallized with ethanol [21].

6- (4- Methyl-phenyl)-2-(morpholin-4-ylmethyl)-4, 5-dihydro (2H)pyridazin-3-one (3a)

6-(4-Methyl-phenyl)-2-(piperazin-1-ylmethyl)-4, 5-dihydro (2H)pyridazin-3-one (4a)

6-(4-Methyl-phenyl)-2-(piperidin-1-ylmethyl)-4, 5-dihydro(2H)pyridazin-3-one (5a)

6- (4- Methyl-phenyl)- 2- [(4-methylpiperazin-1-yl) methyl]-4,5-dihydro(2H)pyridazin-3-one (6a)

6- (4- Methyl-phenyl)- 2- (1, 2-dihydro-10H-phenothiazin-10-ylmethyl)-4,5-dihydro(2H) pyridazin-3-one (7a)

6-(4-Methyl-phenyl)-2-(1H-indol-1-ylmethyl)-4, 5-dihydro(2H)pyridazin-3-one (8a)

6- (4- Methoxy-phenyl)-2-(morpholin-4-ylmethyl)-4,5-dihydro(2H)pyridazin-3-one (3b)

6- (4-Methoxy-phenyl)-2-(piperazin-1-ylmethyl)-4, 5-dihydro(2H)pyridazin-3-one (4b)

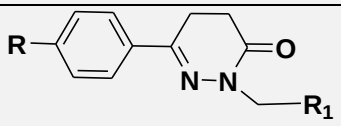
6- (4-Methoxy-phenyl)-2-(piperidin-1-ylmethyl)-4, 5-dihydro(2H)pyridazin-3-one (5b)

6- (4-Methoxy-phenyl)-2-[(4-methylpiperazin-1-yl) methyl]-4,5-dihydro(2H)pyridazin-3-one (6b)

6- (4-Methoxy-phenyl)- 2- (1, 2- dihydro-10H-phenothiazin-10-ylmethyl)-4, 5-dihydro(2H) pyridazin-3-one (7b)

6- (4-Methoxy-phenyl)-2-(1H-indol-1-ylmethyl)-4, 5-dihydro(2H)pyridazin-3-one (8b)

TABLE 1: STRUCTURE OF 6-(SUBSTITUTED PHENYL)-2-(SUBSTITUTED METHYL)-4,5-DIHYDRO (*2H*)PYRIDAZIN-3-ONE DERIVATIVES (3a-8a AND 3b-8b)

S. no.	Compounds	R_1	Structure
1	3a and 3b	N-Morpholinyl	
2	4a and 4b	N-Piperazinyl	
3	5a and 5b	N-Piperidinyl	
4	6a and 6b	N-(4-NMethylpiperazinyl)	
5	7a and 7b	N-Phenothiazinyl	$R=CH_3$ (compounds 3a-8a)
6	8a and 8b	N-Indolyl	$R= OCH_3$ (compounds 3a-8a)

Anti-TB activity using Alamar Blue Dye Assay (MABA): The anti-TB activity of title compounds (3a-8a and 3b-8b) were tested against *M. tuberculosis* H37RV strain using Microplate Alamar Blue Assay (MABA) method. Blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The minimum inhibitory concentration (MIC) was defined as lowest drug concentration which prevented the color change from blue to pink [21, 22].

TABLE 2: PHYSICAL CHARACTERIZATION OF 6-(SUBSTITUTED PHENYL)-2-(SUBSTITUTED METHYL)-4,5-DIHYDRO(*2H*) PYRIDAZIN-3-ONE DERIVATIVES (3a-8a AND 3b-8b)

Compound	Yield (%)	M.P. (ºC)	Molecular Formula	Analytical value					
				Calculated			found		
				C	H	N	C	H	N
3a	68	113- 114	$C_{16}H_{21}N_3O_2$	66.88	7.37	14.62	66.72	7.32	14.56
4a	52	122- 124	$C_{16}H_{22}N_4O$	67.11	7.74	19.56	66.96	7.64	19.50
5a	41	123- 125	$C_{17}H_{23}N_3O$	71.56	8.12	14.72	71.38	7.96	14.52

6a	52	119 -120	$C_{17}H_{24}N_4O$	67.97	8.05	18.65	67.84	7.88	18.54
7a	62	100-102	$C_{24}H_{21}N_3OS$	72.15	5.30	10.52	71.98	5.28	10.36
8a	44	105- 107	C20H19N3O	75.69	6.03	13.24	75.46	5.88	13.12
3b	53	135-136	$C_{16}H_{21}N_3O_3$	63.35	6.98	13.85	63.10	6.88	13.66
4b	46	127-128	$C_{16}H_{22}N_4O_2$	63.55	7.33	18.53	63.38	7.12	18.44
5b	50	132-134	$C_{17}H_{23}N_3O_2$	67.75	7.69	13.94	67.55	7.48	13.76
6b	56	135-137	$C_{17}H_{24}N_4O_2$	64.53	7.65	17.71	64.42	7.53	17.54
7b	60	108-110	$C_{24}H_{21}N_3O_2S$	69.37	5.09	10.11	69.18	4.88	09.92
8b	46	116-118	$C_{20}H_{19}N_3O_2$	72.05	5.74	12.60	71.92	5.54	12.46

TABLE 3: SPECTRAL CHARACTERIZATION OF 6-(SUBSTITUTED PHENYL)-2-(SUBSTITUTED METHYL)-4,5-DIHYDRO(*2H*) PYRIDAZIN-3-ONE DERIVATIVES (3a-8a AND 3b-8b)

Compound	IR (KBr) υmax (cm^{-1})	1H-NMR ($CDCl_3$-d6) δ (ppm)	Ms (m/z)
3a	3012 (CH), 1683 (C=O), 1601 (C=N)	2.28 (s, 3H, CH_3), 2.63 (t, 2H, CH_2), 2.75 (t, 2H, CH_2), 2.93 (m, 4H, 2xCH_2), 3.67 (m, 4H, CH_2-O-CH_2), 4.79 (s, 2H, -N-CH_2-N-), 7.45 (2H, H-3', H-5'), 7.71 (2H, H-2', H-6')	288 (M^++1).
4a	2971 (CH), 1665 (C=O), 1527 (C=C);	2.30 (s, 3H, CH_3), 2.63 (t, 2H, CH_2), 2.91 (t, 2H, 1CH_2), 3.01 (m, 8H, 4xCH_2), 4.77 (s, 2H, -N-CH_2-N-), 7.22 (2H, H-3', H-5'), 7.75 (2H, H-2', H-6'), 9.31 (1H, NH)	287 (M^++1).
5a	2937 (CH), 1661 (C=O), 1421 (C=C);	2.27 (s, 3H, CH_3), 2.61 (t, 2H, CH_2), 2.69 (m, 6H, 3xCH_2), 2.90 (t, 2H, CH_2), 3.01 (m, 4H, 2xCH_2), 5.19 (s, 2H, -N-CH_2-N-), 7.37 (2H, H-3', H-5'), 7.72 (2H, H-2', H-6')	286 (M^++1).
6a	3003 (CH), 1677 (C=O), 1503 (C=N);	2.24 (s, 1H, N-CH_3), 2.39 (s, 3H, CH_3), 2.53 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.13 (m, 4H, 2xCH_2), 3.34 (m, 4H, 2xCH_2), 5.17 (s, 2H, -N-CH_2-N-), 7.41 (dd, 2H, H-3', H-5'), 7.75 (2H, H-2', H-6');	301 (M^++1).
7a	3002 (CH), 1672 (C=O), 1510 (C=N);	2.35 (s, 3H, CH_3), 2.60 (t, 2H, CH_2), 2.98 (t, 2H, CH_2), 5.40 (s, 2H, -N-CH_2-N-), 6.92-7.78 (m, 12H, Ar-H);	400 (M^++1).
8a	2995 (CH), 1681 (C=O), 1573 (C=N);	2.35 (s, 3H, CH_3), 2.65 (t, 2H, CH_2), 2.97 (t, 2H, CH_2), 5.34 (s, 2H, -NCH 2-N-), 7.42-7.79 (m, 10H, Ar-H);	318 (M^++1).
3b	2971 (CH), 1675 (C=O), 1451 (C=C);	2.47 (t, 2H, CH_2), 2.73 (t, 2H, CH_2), 2.91 (m, 4H, 2xCH_2), 3.61 (m, 4H, 2xCH_2), 3.84 (s, 3H, CH_3O), 4.75 (s, 2H, -N-CH_2-N-), 6.93 (dd, 2H, H-3', H-5'), 7.69 (dd, 2H, H-2', H-6');	304 (M^++1).
4b	2971 (CH), 1677 (C=O), 1531 (C=C);	2.61 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.02 (m, 8H, 4xCH_2), 3.83 (s, 3H, CH3O), 4.73 (s, 2H, -N-CH_2-N-), 7.32 (2H, H-3', H-5'), 7.77 (2H, H-2', H-6'), 9.03 (1H, NH)	303 (M^++1)
5b	2997 (CH), 1687 (C=O), 1453 (C=C);	2.61 (t, 2H, CH2), 2.69 (m, 6H, 3xCH_2), 2.85 (t, 2H, CH_2), 2.97 (m, 4H, 2xCH_2), 3.85 (s, 3H, CH_3O), 5.23 (s, 2H, -N- CH_2-N-), 7.45 (2H, H-3', H-5'), 7.79 (2H, H-2', H-6')	302 (M^++1)
6b	2981 (CH), 1686 (C=O), 1591 (C=N);	2.23 (s, 1H, N-CH_3), 2.57 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 3.04 (m, 4H, 2xCH_2), 3.33 (m, 4H, 2xCH_2), 3.87 (s, 3H, CH_3O), 5.25 (s, 2H, -N-CH_2-N-), 7.37 (2H, H-3', H-5'), 7.79 (dd, 2H, H-2', H-6')	317 (M^++1)
7b	2985 (CH), 1663 (C=O), 1601 (C=N);	2.63 (t, 2H, CH_2), 2.98 (t, 2H, CH_2), 3.85 (s, 3H, CH_3O), 5.43 (s, 2H, -N-CH_2-N-), 6.91-7.79 (m, 12H, Ar-H)	416 (M^++1)
8b	3006 (CH), 1682 (C=O), 1605 (C=N);	2.61 (t, 2H, CH_2), 2.99 (t, 2H, CH_2), 3.85 (s, 3H, CH_3O), 5.27 (s, 2H, -NCH 2-N-), 7.33-7.68 (m, 10H, Ar-H)	323 (M^++1).

RESULTS AND DISCUSSION:

Chemistry: Several 6-(substituted phenyl)-2-(substituted methyl)-4,5-dihydro(*2H*)pyridazin-3-one derivatives (3a-8a and 3b-8b) were synthesized according to **Scheme 1**. The acylation of aromatic hydrocarbon(s) with succinic anhydride afforded the aryoyl propionic acid in presence of aluminum chloride. The benzoyl propionic acid on hydrazinolysis gave the 6-phenyl-4,5-dihydro-pyridazinone (2a and 2b). Compounds (3a-8a and 3b-8b) were synthesized by reacting compounds (2a and 2b) with cyclic secondary amine under Mannich reaction conditions. All compounds (3a-8a and 3b-8b) were characterized by spectral data **Table 3**. For example compound 3a, IR spectra (KBr) λmax revealed presence for functional groups CH, C=O and C=N as 3010, 1685 and 1600 cm^{-1}, respectively. The ^{1}H NMR ($CDCl_3$) (ppm) showed singlet for methyl group in phenyl ring at 2.29 (s, 3H, CH_3), two triplets for CH_2-CH_2 in pyridazinone ring at 2.62 (t, 2H, CH_2), 2.76 (t, 2H, CH_2), two multiplates for CH_2-CH_2 in piperazine ring at 2.95 (m, 4H, 2×CH_2), 3.69 (m, 4H, CH_2-O-CH_2), one singlet for methylene bridge between pyridazinone and piperazine ring at 4.78 (s, 2H, -N-CH_2-N-), two multiplates for phenyl ring 7.43 (2H, H-3', H-5'), 7.73 (2H, H-2', H-6'). Mass spectra were obtained (m/e) ion peak at 288 (M^++1).

Elementary analyses gave satisfactory results and values were in the range of ±0.4% theoretical value for the element analyzed or calculated (C, H, N). Other compounds were also elucidated in the same manner.

TABLE 4: ANTITUBERCULAR ACTIVITY OF 6-(SUBSTITUTED PHENYL)-2-(SUBSTITUTED METHYL)-4,5-DIHYDRO(*2H*) PYRIDAZIN-3-ONE DERIVATIVES (3a-8a AND 3b-8b) AGAINST *M. TUBERCULOSIS* H37Rv STRAIN BY MABA METHOD

S. no.	Compound	MIC (µg/mL)
1	3a	25
2	4a	12.5
3	5a	12.5
4	6a	25
5	7a	6.25
6	8a	12.5
7	Pyrizinamide	3.12
8	3b	12.5
9	4b	12.5
10	5b	25
11	6b	12.5
12	7b	6.25
13	8b	12.5
14	Streptomycin	6.25

Antitubercular Evaluation: The anti-TB screening was carried out against *M. tuberculosis* H_{37}Rv by MABA method **Table 4**. The results illustrated that (7a) and (7b) were showed best antitubercular activity among the synthesized compounds with MIC-6.25 µg/mL. Seven compounds, (4a, 5a, 8a, 3b, 4b, 6b and 8b) were also significant in their anti-TB action with MIC values 25 µg/mL. Rest of the compounds (3a), (6a) and (5b) were showed MIC values of 25µg/mL. Pyridazinone derivatives having phenothiazine ring (7a and 7b) were found to have better activity than other pyridazinone compounds.

After pheno-thiazine heterocyclic ring compounds, Piperazine (4a and 4b) and Indole (8a and 8b) ring contain compounds were found more active than other remaining compounds. Reference drugs, Pyrizinamide (PZA) and Streptomycin (STR) were showed MIC value 3.125 µg/ml and 6.25 µg/ml, respectively.

Structure Feature of Pyridazinone Derivatives: Pyridazinone derivatives hold considerable interest in all types of biological activities. Various structural modifications were carried out in pyridazinone ring system and these structural changes cause some fruitful biological activities [20-22]. From the above findings wed developed some pyridazinone compounds as antitubercular agents. First-line antitubercular agents like isoniazid and pyrizinamide have carbonylhydrazide, amide group, aryl ring, pyridine, and pyrazine. All these chemical moieties are present in synthesized pyridazinone compounds. Currently, various pyridazinone compounds are presently under investigation. These compounds have been shown anti-TB activity.

CONCLUSION: The study showed the anti-tubercular potential of pyridazinones. A variation in the substitution of the pyridazine ring often causes a marked difference in the biological activities. Currently, much attention has been focused on the pyridazine attached with another heterocyclic ring, which has a useful structure for molecular exploration and for the development of active compounds with different biological activities.

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