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Synthesis and biological evaluation of anti-tubercular activity of some synthesised pyrazole derivatives

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Abstract

In the development of organic therapeutic agents, pharmaceutical scientists have explored numerous approaches in finding and developing organic compounds that are now available to us in dosage forms suitable for the treatment of our ills and often for the maintenance of our health. The present work deals with evaluation of anti-tubercular activity of various aldehyde derivatives synthesized by Claisen-Schmidt condensation method. The formation of pyrazole derivatives by reaction with phenyl isothiocyanate was also attempted. The synthesized derivatives were screened for anti-tubercular activity and the compounds demonstrated some remarkable features to be actively considered as anti-tubercular drugs.

Keywords : Pyrazolines, antimycobacterial agents.

Introduction

Tuberculosis, one of the oldest diseases known to affect humans, is caused by bacteria belonging to the *Mycobacterium tuberculosis* complex, an acid-fast aerobic bacillus. It is estimated that today one-third to one-half of the world population is infected with *Mycobacterium tuberculosis* leading to approximately 6% of all death worldwide.

Tuberculosis is the leading worldwide cause of mortality resulting from an infectious bacterial agent. *Mycobacterium tuberculosis* is transmitted primarily via the respiratory route. Tuberculosis is a disease, which mainly affects the lungs (80-85% of the case); although in up to one-third of cases other organs are involved. It is the most frequent cause of death worldwide due to single infectious agent, and in 1993 WHO declared Tuberculosis as a global public health emergency. The physician is greatly challenged to provide optimal therapy for Mycobacterial illness because of the advent of AIDS, the increase in both drug-susceptible and multidrugresistant tuberculosis,

and the plethora of new antibiotics with antimycobacterial potential[1-4]. The aim of chemotherapy of tuberculosis is

1. To kill the dividing bacilli in the lung lesions.
2. To kill the persisters.

Pure organic compounds, natural and synthetic are the chief source of agents for the cure, the mitigation or the prevention of disease today. These agents have had their origin in a number of ways, *viz.*, (a) from naturally occurring materials of both plant and animal origin, (b) from the synthesis of organic compounds whose structure are closely related to those of naturally occurring compounds, and (c) that of pure synthetic has provided significant discoveries of medicinal chemistry[5]. Tuberculosis has recently reemerged as a major health concern. Each year, approximately 2 million persons worldwide die of tuberculosis and 9 million become infected.[6]In the United States, approximately 14000 cases of tuberculosis were reported in 2006, a 3.2% decline from the previous year; however, 20 states and the District of Columbia had higher rates.[7] The prevalence of tuberculosis is continuing to increase because of the increased number of patients infected with human immunodeficiency virus, bacterial resistance to medications, increased international travel and immigration from countries with high prevalence, and the growing numbers of the homeless and drug abusers.[8]With 2 billion persons, a third of the world population, 1 estimated to be infected with mycobacteria, all nurses, regardless of area of care, need to understand the pathophysiology, clinical features, and procedures for diagnosis of tuberculosis. The vulnerability of hospitalized patients to tuberculosis is often underrecognized because the infection is habitually considered a disease of the community. Most hospitalized patients are in a suboptimal immune state, particularly in intensive care units, making exposure to tuberculosis even more serious than in the community. By understanding the causative organism, pathophysiology, transmission, and diagnostics of tuberculosis and the clinical manifestations in patients, critical care nurses will be better prepared to recognize infection, prevent transmission, and treat this increasingly common disease.

Causative Organism

Tuberculosis is an infection caused by the rod-shaped, non-spore-forming, aerobic bacterium *Mycobacterium tuberculosis*. [9] Mycobacteria typically measure 0.5 μm by 3 μm , are classified as acid-fast bacilli, and have a unique cell wall structure crucial to their survival. The welldeveloped cell wall contains a considerable amount of a fatty acid, mycolic acid, covalently attached to the underlying peptidoglycan-bound polysaccharide arabinogalactan, providing an extraordinary lipid barrier. This barrier is responsible for many of the medically challenging physiological characteristics of tuberculosis, including resistance to antibiotics and host defense mechanisms.

The composition and quantity of the cell wall components affect the bacteria's virulence and growth rate. The peptidoglycan polymer confers cell wall rigidity and is just external to the bacterial cell membrane, another contributor to the permeability barrier of mycobacteria. Another important component of the cell wall is lipoarabinomannan, a carbohydrate structural antigen on the outside of the organism that is immunogenic and facilitates the survival of mycobacteria within macro - phages. The cell wall is key to the survival of mycobacteria, and a more complete understanding of the biosynthetic pathways and gene functions and the development of antibiotics to prevent formation of the cell wall are areas of great interest.

Transmission

Mycobacterium tuberculosis is spread by small airborne droplets, called droplet nuclei, generated by the coughing, sneezing, talking, or singing of a person with pulmonary or laryngeal tuberculosis. These minuscule droplets can remain airborne for minutes to hours after expectoration. The number of bacilli in the droplets, the virulence of the bacilli, exposure of the bacilli to UV light, degree of ventilation, and occasions for aerosolization all influence transmission. Introduction of *M tuberculosis* into the lungs leads to infection of the respiratory system; however, the organisms can spread to other organs, such as the lymphatics, pleura, bones/joints, or meninges, and cause extrapulmonary tuberculosis

Materials and methods

Experimental Section:

Melting points were determined in open capillary tubes and are uncorrected. IR spectra carried out on Perkin-Elmer FTIR spectrophotometer (cm^{-1} , in KBr). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker spin spectrometer (400 MHz) in CDCl_3 and TMS was used as internal standard. Peak values are shown in ppm, in the δ scale. Mass spectra were recorded on a Waters LC-MS. Elemental analyses were carried out on Perkin-Elmer analyzer.

General procedure for 3-(substituted phenyl)-1-phenylprop-2-en-1-one(3a-c).

A mixture of acetophenone (1.5017 g, 0.01 mmol), appropriate aldehyde (0.01 mmol) in ethanol and sodium hydroxide (30%, 5 mL) in presence of 10 mL of petroleum ether was stirred under room temperature for 4 h. The resulting solution was allowed to stand overnight and poured into ice-cold water, then it was neutralized with hydrochloric acid. The solid so obtained was filtered, dried and crystallized from ethanol.

General procedure for 5-(substituted phenyl)-3-phenyl-4,5-dihydro-1H-pyrazole(4a-c).

To a solution of chalcone (3a-c) in ethanol, hydrazine hydrate (99%) was added dropwise. The reaction mixture was heated under reflux for 7 h and then cooled and poured onto crushed ice. The solid pyrazoline product was filtered and recrystallized from ethanol.

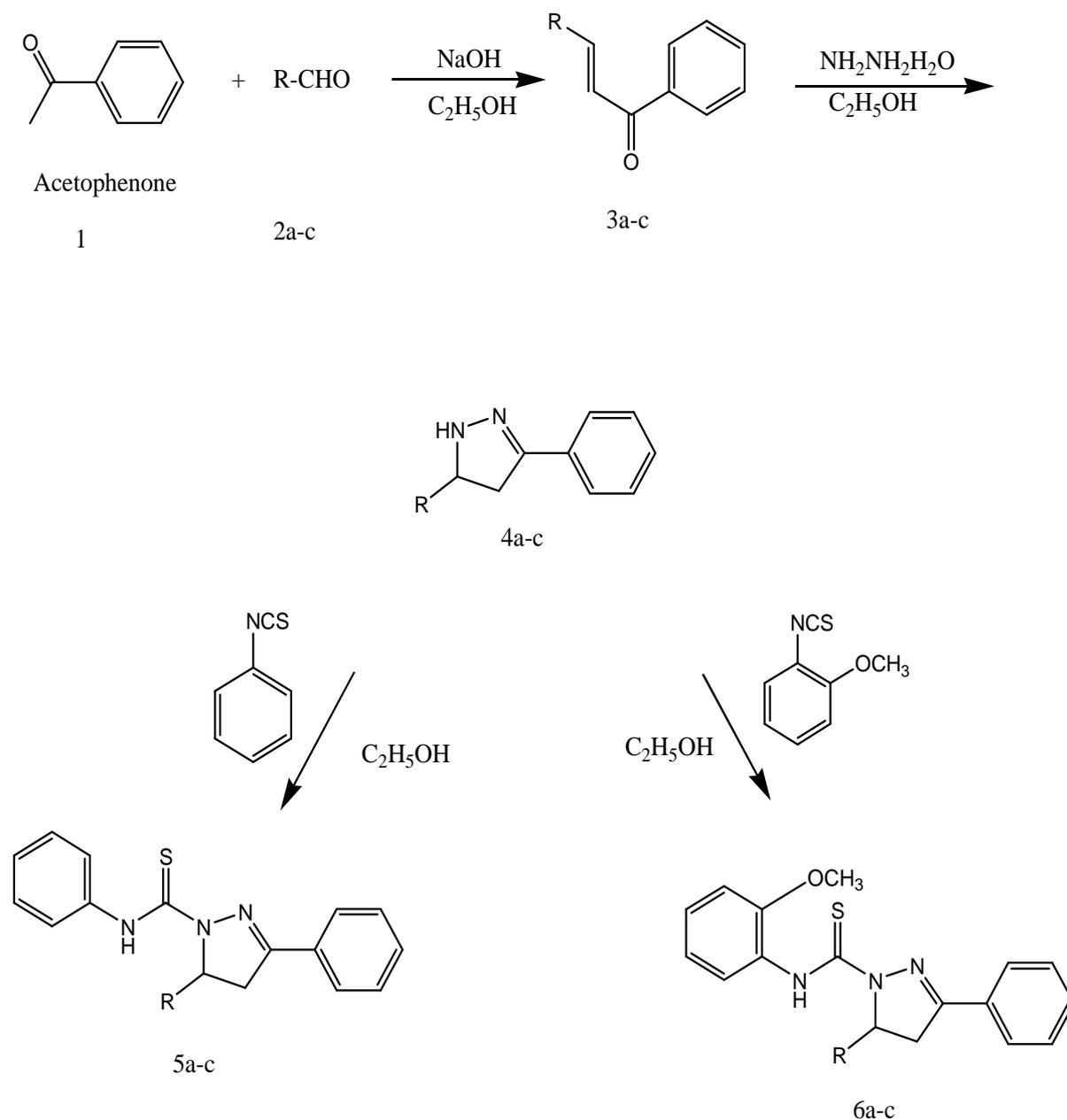
General procedure for 5-(substituted phenyl)-N-(2-methoxyphenyl)-3-phenyl-4,5-dihydro pyrazole-1-carbothioamide(5a-c).

1-isothiocyanatobenzene (0.01 mol) was added to a solution of pyrazoline (4a-c) (0.01 mol) in ethanol (20 mL). The reaction mixture was refluxed for 4 h and after cooling it was poured onto crushed ice. Then, the separated solid mass was filtered, washed with water and crystallized from ethanol.

General procedure for 5-(substituted phenyl)-N,3-diphenyl-4,5-dihydropyrazole-1-carbo thioamide(6a-c).

To a solution of pyrazoline (4a-c) in ethanol (20 mL) 1-isothiocyanato-2-methoxybenzene (0.01 mol) was added and the reaction mixture was refluxed for 4 h. Then, after cooling, the reaction mixture was poured onto crushed ice and the separated solid mass was filtered, washed with water and crystallized from ethanol.

Scheme



Result and Discussion

Physical characteristics of synthesised compounds

Compound No.	R	Yield (%)	M.P. ($^{\circ}\text{C}$)	Mol.formula	Mol.weight	R_f
3a	2-Cl phenyl	74	42-44	$\text{C}_{15}\text{H}_{11}\text{ClO}$	242.7	0.4
3b	p-hydroxy phenyl	70	120	$\text{C}_{15}\text{H}_{12}\text{O}_2$	224.25	0.6
3c	cinnamaldehyde	72	98-100	$\text{C}_{17}\text{H}_{14}\text{O}$	234.29	0.2
4a	2-Cl phenyl	80	70	$\text{C}_{15}\text{H}_{13}\text{ClN}_2$	256.73	0.7
4b	p-hydroxy phenyl	82	118	$\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$	238.28	0.3
4c	cinnamaldehyde	92	160	$\text{C}_{17}\text{H}_{16}\text{N}_2$	248.32	0.1
5a	2-Cl phenyl	85	58-60	$\text{C}_{22}\text{H}_{18}\text{ClN}_3\text{S}$	391.92	0.5

5b	p-hydroxy phenyl	77	178-180	C ₂₂ H ₁₉ N ₃ OS	373.47	0.3
5c	cinnamaldehyde	82	128-130	C ₂₄ H ₂₁ N ₃ S	383.51	0.7
6a	2-Cl phenyl	90	58-60	C ₂₃ H ₂₀ ClN ₃ OS	421.94	0.4
6b	p-hydroxy phenyl	75	138-140	C ₂₂ H ₂₀ N ₃ O ₂ S	390.48	0.6
6c	cinnamaldehyde	76	150-152	C ₂₅ H ₂₃ N ₃ OS	413.53	0.2

Spectral data of synthesised compounds

Compound Code	IR(cm ⁻¹ ,KBr)	Mass (m/e)	¹ H NMR (CDCl ₃ ,ppm)
1	~3220(NH), ~1590(C=N), ~1320(C-N), ~1130(C=S), ~748(C-Cl)	390.3(M+), 392.0 (M+2)	1.2(3H,s),2.1(1H,s),6.8(2H,t), 7.0(1H,t),7.5(5H,m),
2	~3220(NH), ~1590(C=N), ~1320(C-N), ~1130(C=S), ~3307(OH)	372.1(M+) 374.6(M+2)	1.2(3H,S),2.1(1H,S),6.9(2H,d) 7.2(1H,t),7.5(5H,q)3.4(2H,d)
3	~3220(NH), ~1590(C=N), ~1320(C-N), ~1130(C=S), ~1600(C=C)	382.3(M+) 384.1(M+2)	3.9(1H,s),3.8(1H,t),7.7(2H,d), 7.4(2H,t),2.1(1H,s)
4	~3220(NH), ~1590(C=N), ~1320(C-N), ~1130(C=S), ~748(C-Cl)	420.2(M+) 422.1(M+2)	7.5(5H,m),7.3(3H,t),7.2(2H,m), 3.2(2H,d),3.8(1H,q)
5	~3220(NH), ~1590(C=N), ~1320(C-N), ~1130(C=S), ~3307(OH)	389.2(M+) 391.1(M+2)	3.8(1H,q),3.2(2H,d),7.5(5H,m), 3.2(1H,d),3.9(1H,s)
6	~3220(NH), ~1590(C=N), ~1320(C-N), ~1130(C=S), ~1600(C=C) .	412.8(M+) 414.1(M+2)	7.8(4H,m),3.8(1H,t),3.2(2H,d), 7.5(5H,m),6.8(1H,S)

Conclusion

5-(2-Chloro phenyl)-N,3-diphenyl-4,5-dihydropyrazole-1-carbothioamide is better yield compare to other synthesized compounds.

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