SYNTHESIS OF NOVEL HETEROCYCLIC QUINOLONE COMPOUND FOR ANTI -TUBERCULAR ACTIVITY

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ABSTRACT

In last few decades, though significant progress has been made in the treatment and control strategies of tubercular infections by introducing new diagnostic and monitoring tools and combination therapy, it still continues to be severe problem. The need of study was only because of there are many drugs in market to treat infection but most of the drugs are showing resistance because of the same it is difficult to treat the infection. In this study we chosen quinolone nucleus for study and over it. Thus with the aim of developing novel molecule with improved potency for treating *Mycobacterium tuberculosis* H37Rv strain infections and with decreased probability of developing drug resistance. **Methodology:** The synthesis of Quinolone derivatives, starting from substituted aniline and ethyl acetoacetate, by conventional organic reaction and results of investigations of their anti-mycobacterial activity. **Results:** MICs of the synthesized compounds are compared with existing drugs Cytotoxicity. The substituted quinolones are synthesized by taking mixture of 7-substituted-2-(3-chloro-2-oxopropyl) quinolin-4(1H)-one and different secondary amines. Many compounds have shown promising activity while some were inactive. **Conclusion:** It was found that Compound A_1, A_3, B_1, B_3, have shown promising anti tubercular activity whereas compound A_2, A_4,B_2,B_4 were showing moderate anti tubercular activity against std. Streptomycin.

KEYWORDS: Quinolone derivative; Well diffusion method; Spectral analysis; Elemental analysis.

INTRODUCTION

Microbial infections remain the major cause of death over the world. Emergence of multi-drug resistant to different infectious organisms like *M. tuberculosis* made the condition most alarming.[1-2] Tuberculosis, MTB, or TB is a deadly infectious disease caused by various strains of mycobacteria; usually Mycobacterium tuberculosis. According to World Health Organization (WHO) TB is a global pandemic, which has become an important world-wide public health menace with one-third of the world's population infected by the TB bacillus. Most infections do not have symptoms, known as latent tuberculosis and about one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those so infected. People with weak immune systems (those with HIV/AIDS, those receiving immunosuppressive drugs and chemotherapy) are at a greater risk for developing TB disease. There is currently a growing concern about the progress and spread of multidrug and extensively drug resistant tuberculosis (MDR/XDR -TB), which has the potential to paralyze TB care schemes. The focal theme of this thesis is the exploration of new strategies in the field of modern drug discovery for the development of new drugs, which are capable of overcoming MDR/XDR-TB. The present work was aimed to synthesized new compound and evaluate it for antituberculer activity. Therefore, there is an urgent demand for a new class of antimicrobial agent with a different mode of action and it led medicinal chemists to explore a wide variety of chemical structures.

Quinoline was first isolated from coal tar in 1834, it was also recognized as pyrolytic degradation product of cinchonamine, an alkaloid closely related to quinine[3-6]. The name quinoline was derived from *quina,* a Spanish version of a local South American name for the bark of quinine-containing *cinchona* Species. Several Synthetic anti-malarial drugs are based on the quinoline nucleus, Chloroquine is an example. Several antibiotics like fluro-quinolones now in clinical use were 4-quinolone-based antibiotics.[7-10] Quinoline is a color-

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less liquid of bp. 237^{0}C. It turns yellow on standing and has pyridine like smell.Miscible with most organic solvents and dissolves in water to about 0.7 % at room temperature. Slightly weaker base (pK_a= 4.94) than pyridine (pK_a= 5.2). It reacts with acid to yield salts which are sparing soluble in water[11-12].

Compounds containing quinolones exhibiting variety of pharmacological and biological activities[13-25].

Experimental

General: The nucleus and its derivatives were analyzed by different ways. The melting points were recorded on electrothermal apparatus and are uncorrected.(IR) spectra were determined on Bruker IFS-66 FTIR (Bruker Bioscience, USA) using KBr pallets and wave number (ί) was reported in cm-1. ^{1}H NMR spectra on a Bruker Avance 300 MHz instrument using DMSO as solvent using TMS as internal standard; the chemical shifts (δ) were reported in ppm with coupling constants (*J*) are given in Hz. Signal multiplicities were represented by s (singlet), d (doublet), t (triplet), ds (double singlet), dd (double doublet), m (multiplet) and bs (broad singlet. Elemental analysis was performed on a Hera- cus CHN-Rapid Analyzer. Analysis indicated by the symbols of the elements of functions was within ±0.4% of the theoretical values. The purity of the compounds was checked on silica gel coated Al plates (Merck).

Synthesis of 2-methyl-7-substituted-4-quinolone

A mixture of (0.01 mol) substituted anilines and (0.01 mol) ethyl acetoacetate was stirred, was heated on oil bath at 180^{0}C for two hours, The crude solid was filtered, dried and recrystallized from ethanol .

2. Synthesis of 7-substituted-2-(3-chloro-2-oxopropyl) quinolin-4(1H)-one (II)

An quantity of 0.01 moles of **I** was dissolved in 25 ml of glacial acetic acid. If did not dissolve completely, the mixture was slightly warmed. The solution was cooled in ice bath with stirring. To this chloroacetyl chloride (0.12 mole) solution added drop wise. To prevent the occurrence of vigorous reaction the temp was maintained at 0^{o}C then reaction was heated for 30 mins after this cool the mixture and pour over crushed ice white product was separated by filtration. The product was washed with 50% aqueous acetic acid and finally with water. It was recrystallized.

3. **Synthesis of derivatives of substituted 4-quinolones III**

A mixture of 0.01 mole of each **II** were taken in dry 250 ml round bottom flask separately to this distilled alcohol is added as solvent and to this different secondary amines were added in 0.01 mole concentrations and refluxed for 2 hour after reflux add reaction mixture to crushed ice precipitation formed is filtered and recrystallized.

Spectral Data

A_1- IR (KBr): 3487.07 (-N-H str), 3032.16 (Ar-H str), 2841 (CH str), 1721 (-C=O str), 1685 (CO str amide), 1160 (-C-N str), 801(-C-Clstr) NMR: d8.5-8.(0 1H, S-NH), 7.91-7.87 (4H ,*m*-Quinolone), 7.37-6.97 4H,*m* -Ar-CH 3.81-3.12 2H,*d* -CH_2

A_2- IR (KBr): 3487.07 (-N-H str), 3135(Ar-H str), 2561 (CHstr), 1721 (-C=O str), 1685 (CO str amide), 1353 (–SO2NH2 str), 1200 (-C-N str) 801(-C-Clstr)

A_3- IR (KBr): 3372 (-N-H str), 3032(Ar-H str), 2850 (CHstr), 1720 (-C=O str), 1685 (CO str amide), 1200 (-C-N str) 780 (-C-Clstr)

A_4- IR (KBr):3420 (-OH str), 3380 (-N-H str), 3020(Ar-H str), 2862 (CHstr), 1700 (-C=O str), 1685 (CO str amide), 1230 (-C-N str) 759 (-C-Clstr)

B_1- IR (KBr):3367 (-NH str), 3021 (-Ar-H str), 2848(-CH str), 1728 (-C=O str), 1655 (CO str amide), 1157 (-C-N str) 662 (-C-Br str)

B_2- IR (KBr):3367 (-NH str), 3021 (-Ar-H str), 2848(-CH str), 1728 (-C=O str), 1655 (CO str amide), 1353 ((–SO2NH2 str))1157 (-C-N str) 662 (-C-Br str)

B_3- IR (KBr): 3372 (-N-H str), 3032(Ar-H str), 2850 (CHstr), 1720 (-C=O str), 1685 (CO str amide), 1200 (-C-N str) 645 (-C-BR str)

B_4- IR (KBr):3420 (-OH str), 3370 (-N-H str), 3020(Ar-H str), 2850 (CHstr), 1690 (-C=O str), 1680 (CO str amide), 1230 (-C-N str) 650 (-C-Br str)

Anti-tubercular activity: The compounds were tested in-vitro for their anti-tubercular activity against H_{37}Rv Strain.

Method: **Alamar Blue Dye:** The anti-tubercular screening was carried out by Middle brook 7H9 agar medium against H_{37}Rv Strain. 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

Scheme: (A_1-A_4, B_1-B_4)

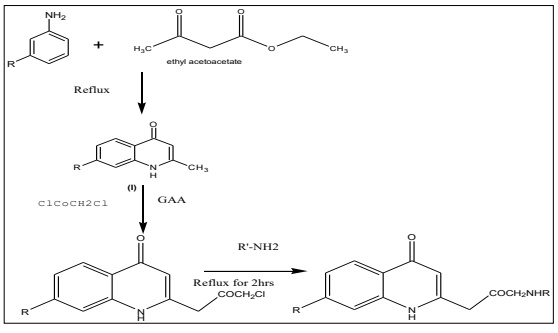


Table 1. Derivative compounds

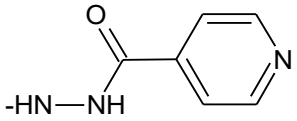
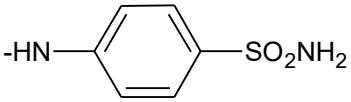
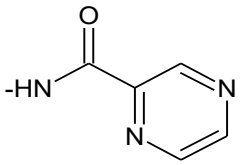
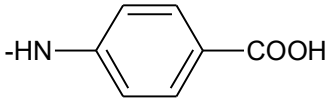
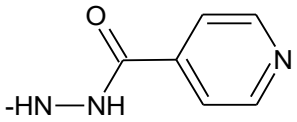
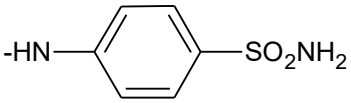
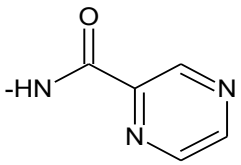
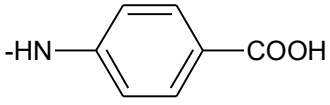
Compounds	R	R'
A_1	-Cl	
A_2	--Cl	
A_3	--Cl	
A_4	--Cl	
B_1	- Br	
B_2	- Br	
B_3	- Br	
B_4	- Br	

Table 2. Anti-tubercular activity of substituted 4-quinolones compounds

Comp ID	100	50	25	12.5	6.25	3.125	1.6	0.8	0.4	0.2
A1	S	S	S	S	S	S	S	R	R	R
A2	S	S	S	S	R	R	R	R	R	R
A3	S	S	S	S	S	S	S	S	R	R
A4	S	S	S	R	R	R	R	R	R	R
B1	S	S	S	S	S	S	S	R	R	R
B2	S	S	S	S	S	R	R	R	R	R
B3	S	S	S	S	S	S	S	S	S	R
B4	S	S	S	S	R	R	R	R	R	R
Strepto-mycin	S	S	S	S	S	R	R	R	R	R

Table 3. Analytical data of the compound

Comp. Code	Mol. Formula	Mol. Wt.	m.p. ° C	Yield %	R_f val-ue	Elemental analyses Calcd. (Found)		
						C	H	N
A_1	$C_{18}H_{15}ClN_4O_3$	370.78	180-182	79.85	0.50	58.31	4.08	15.11
A_2	$C_{18}H_{16}ClN_4O_4S$	405.85	142-144	72.53	0.57	53.27	3.97	10.35
A_3	$C_{17}H_{13}ClN_4O_3$	356.76	130-132	69.52	0.53	57.23	3.67	15.70
A_4	$C_{18}H_{22}ClN_3O_4$	379.83	136-138	74.54	0.50	56.92	5.84	11.0
B_1	$C_{18}H_{15}BrN_4O_3$	415.24	110-112	75.34	0.61	52.06	3.64	13.49
B_2	$C_{18}H_{16}BrN_3OS$	450.30	140-142	74.67	0.59	48.01	3.58	9.33
B_3	$C_{17}H_{13}BrN_4O_3$	401.21	112-114	72.23	0.65	50.89	3.27	13.9
B_4	$C_{18}H_{22}BrN_3O_4$	424.28	136-138	62.12	0.64	50.95	5.23	9.90

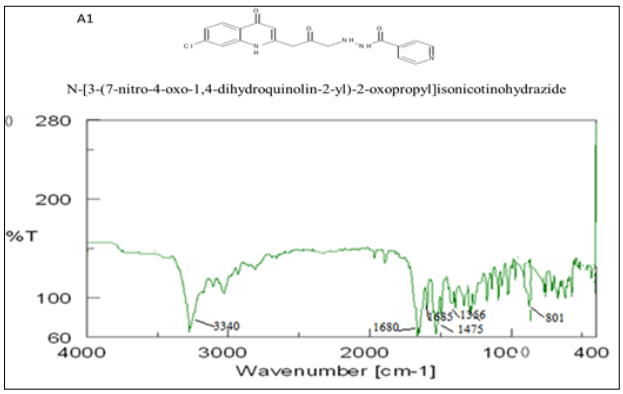


Figure 1. IR Spectra of A_1

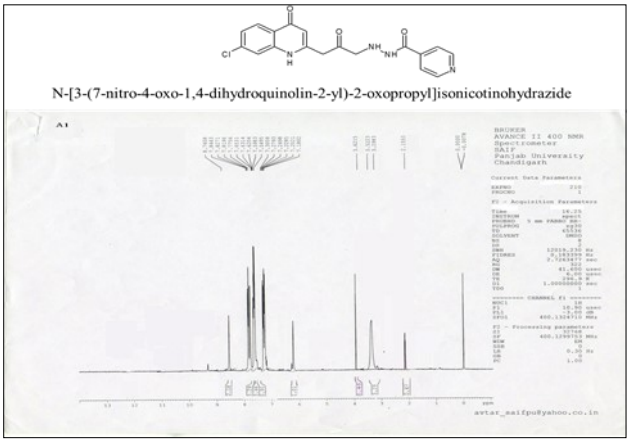


Figure 2. NMR Spectra of A_1

DISCUSSION:

In the present research work, we have synthesized 8 new substituted 4-quinolones derivatives as explained in the scheme. The purity of the compounds was checked by TLC and melting point. Structures of these compounds were confirmed by IR, 1HNMR and elemental analysis. The synthesized compounds were subjected to anti tubercular activity by Alamar Blue Dye method against the standard streptomycin.

Compound A_1, A_3, B_1, B_3 have shown promising antitubercular activity against streptomycin at concentration of 1.6 mcg/ml by interpreting data of MIC. With the suitable molecular modification and manipulation with possible SAR studies of these compounds, promising anti tubercular agents can be obtained. [26, 27].

CONCLUSION

The substituted quinolones are synthesized by taking mixture of 7-substituted-2-(3-chloro-2-oxopropyl) quinolin-4(1H)-one and different secondary amines. It was found that Compound A_1, A_3, B_1, B_3, have shown promising anti tubercular activity whereas compound A_2, A_4,B_2,B_4 were showing moderate anti tubercular activity against std. Streptomycin.

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