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In-Vitro Antitubercular Activity of Some Novel 6-Substituted/ Unsubstituted-2-Phenyl-Quinoline Derivatives

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Original Research Article

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Abstract: With an objective to develop some potent, novel and less side effect having antitubercular agents here we have synthesized a series of substituted/ unsubstituted 2-phenyl tetrahydroquinoline derivatives (IIa-g). These were obtained by the reaction between substituted 2-phenyl-1, 2, 3, 4- tetrahydroquinoline and sulphur in acetonitrile. Structure of the newly synthesized compounds were confirmed on the basis of physico-chemical and spectral data (IR, ^{1}H NMR, ^{13}C NMR and Mass). All the synthesized compounds were screened for their antitubercular activity using Microplate Alamar Blue Assay (MABA) method. Among the synthesized compounds II b, II e and II g have shown significant antitubercular activity.

Keywords: Quinoline, acetonitrile, antitubercular, MABA and isoniazid.

INTRODUCTION

Tuberculosis (TB) is one of the chronic infectious diseases. It is caused by *Mycobacterium tuberculosis.* With nearly one-third of the global population infected with the *Mycobacterium tuberculosis* bacilli, it is still a major cause of mortality and morbidity. According to the World Health Organization (WHO) facts sheets, TB kills 2 million people each year. It is estimated that between 2000 and 2020, nearly one billion people will be newly infected if control is not further strengthened [2, 1]. The situation has become worst due to the development of multi drug resistant TB (MDR-TB) and extensive drug resistant –TB (XDR-TB), which are resistant to first line and second line TB drugs. Recent WHO updates claim that approximately 9.6% of all MDR-TB cases are XDR-TB [2]. Therefore, there is an urgent need for the development of new anti-TB agents to effectively combat TB.

In this research work we have selected quinoline as the parent moiety due to its versatile pharmacological and biological properties like antitubercular [3-5], antimalarial [6-8], antimicrobial [9], anti-inflammatory [10, 11], anticancer [12-14], antiviral [15], antioxidant [16], antileishmanial [17], analgesic [18], antifungal [19], anti-convulsant and antihypertension [20] activities.

Therefore, in view of the above facts and in continuation with our research work on quinoline derivatives as antitubercular agents, here we have reported the synthesis, spectral studies and anti-TB activity screening of some novel quinoline derivatives.

The spectral data of the compounds IIa-g shows Characteristic IR peaks for C=N in the range of 1620 cm^{-1}; ^{1}H NMR shows multiplet around 7.36-7.43 δ ppm for C_3 & C_6-quinoline & Ar-H and in the range of 7.93-8.07 for C_8-quinoline & Ar-H.

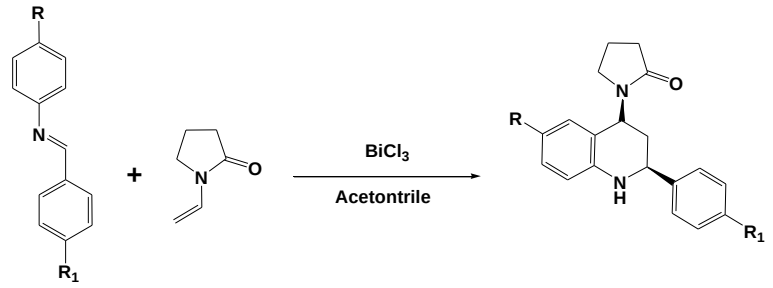
BIOLOGICAL ACTIVITY

Antitubercular activity

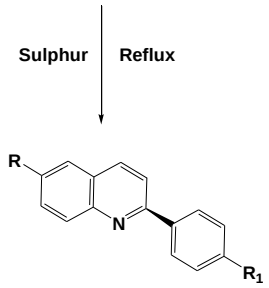
MIC values were determined for the newly synthesized compounds against *M. tuberculosis* strain H_{37}Rv using the Microplate Alamar Blue assay (MABA) [21], using isoniazid as the standard drug. The 96 wells plate received 100 µl of Middlebrook 7H9 broth and serial dilution of compounds were made directly on the plate with drug concentrations of 0.2, 0.4, 0.8, 1.6, 3.125, 6.25, 12.5, 25, 50 and 100 µg/ml. Plates were covered and sealed with parafilm and incubated at 37ºC for 5 days. Then, 25 µl of freshly prepared 1:1 mixture of almar blue reagent and 10% Tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth and pink color was scored as growth. The MIC was defined as the lowest drug concentration, which prevented color change from blue to pink. Compounds showed antitubercular activity between MIC of >100- 6.25 µg/ml.

EXPERIMENTAL PROTOCOL

Scheme



I (a-g)



II (a-g)

Compound	R	R_1
II a	H	H
II b	H	Cl
II c	F	H
II d	Br	NO_2
II e	CH_3	H
II f	OCH_3	H
II g	OCH_3	F

General procedure for the synthesis of 2-phenyl quinolines II (a-g)

To a solution of substituted 2-phenyl-1, 2, 3, 4-tetrahydroquinolines (Ia-g) (1 mmol) in acetonitrile (10 ml), 5g sulphur was added. The reaction mixture was refluxed for 3 h. After completion of the reaction, (as indicated by TLC), the mixture was diluted with 100 ml water and extracted with ethyl acetate (2 x 20 ml), dried over anhydrous Na_2SO_4 and evaporated. The crude compounds were purified by column chromatography with petroleum ether-ethyl acetate (9:1) as eluent.

II a: IR (KBr, cm^{-1})

1612 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm); 7.28-7.44 (m, 5H, C_3, C_6-quinoline & Ar-H), 7.61-7.68 (m, 2H, C_5 & C_7-quinoline), 7.72 (d, 1H, C_4-quinoline), 7.99-8.05 (m, 3H, Ar-H & C_8-quinoline); ^{13}C NMR (400 MHz, $CDCl_3$ δ ppm) 120.0, 126.0, 127.5, 127.7, 127.9, 127.9, 128.9, 129.8, 130.3, 130.3, 130.9, 137.0, 138.6, 148.0, 157.0.; MS m/z (%) = 207 (M+1);

II b: IR (KBr, cm^{-1})

1616 (C=N) ; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm); 7.29-7.42 (m, 4H, C_6-quinoline & Ar-H), 7.31-7.38 (m, 2H, C_5 & C_7-quinoline), 7.42 (d, 1H, C_3-quinoline), 7.98-8.03 (m, 3H, Ar-H & C_8-quinoline); MS m/z (%) = 240 (M+1).

II c: IR (KBr, cm^{-1})

1620 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm); 7.36-7.43 (m, 4H, C_3 & C_6-quinoline & Ar-H), 7.61-7.75 (m, 3H, C_4, C_5 & C_7-quinoline), 7.93-8.07 (m, 3H, C_8-quinoline & Ar-H); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm); 110.7, 119.2, 120.4, 127.1, 127.6, 127.8, 127.8, 130.2, 130.2, 131.8, 137.0, 138.0, 145.1, 156.2, 161.2.; MS m/z (%) = 224 (M+1).

II d: IR (KBr, cm^{-1})

1610 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm; 7.49 (d, 1H, C_3-quinoline), 7.72-7.78 (m, 2H, C_7 & C_8 -quinoline), 7.92-7.98 (m, 2H, C_4 & C_5 -quinoline); 8.25-8.28 (m,4H, Ar-H); MS m/z (%) = 329 (M+1).

II e: IR (KBr, cm^{-1})

1622 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm); 3.83 (s, 3H, OCH_3), 6.98 (s, 1H, C_5 -quinoline), 7.28-7.35 (m, 4H, C_7 -quinoline & Ar- H), 7.42 (d, 1H, C_3 -quinoline), 7.65-7.69 (d, 1H, C_4 -quinoline), 8.06-8.15 (m, 3H, Ar-H & C_8-quinoline); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm); 56, 106.2, 120.5, 123.0, 127.0, 127.6, 127.8, 127.8, 130.2, 130.2, 131.3, 136.8, 137.6, 143.0, 155.3, 158.1; MS m/z (%) = 220 (M+1).

II f: IR (KBr, cm^{-1})

1610 (C=N) ; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm); 2.35 (s, 3H, CH_3), 7.27-7.34 (m, 3H, Ar-H), 7.41 (d, 1H, C_3-quinoline), 7.48 (m, 2H, C_5 & C_7-quinoline), 7.69 (d, 1H, C_4-quinoline), 7.99-8.05 (m, 3H, Ar-H & C_8-quinoline); MS m/z (%) = 236 (M+1).

II g: IR (KBr, cm^{-1})

1614 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm); 3.75 (s, 3H, OCH_3), 6.96 (s, 1H, C_3 -quinoline), 7.06 (m, 2H, Ar-H), 7.33 (d, 1H, C_7 -quinoline), 7.42 (d, 1H, C_3 -quinoline), 7.64 (d, 1H, C_4 -quinoline), 8.05-8.12 (m, 3H, Ar-H & C_8 -quinoline); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm); 56, 106.3, 116.5, 116.5, 120.5, 123.0, 127.0, 129.3, 129.3, 130.8, 131.5, 137.4, 142.6, 155.2, 158.0, 162.0; MS m/z (%) = 254 (M+1).

RESULTS AND DISCUSSION

Table-1: Physico-chemical data of the synthesized compounds II (a-g)

Compound	Molecular formula	M.P ^{0}C	%Yield	Elemental Analysis Found (Calcd) %		
				C	H	N
II a	$C_{15}H_{11}N$	112-114	68	87.77 (87.74)	5.30 (5.28)	6.52 (6.50)
II b	$C_{15}H_{10}ClN$	104-106	71	75.16 (75.14)	4.21 (4.19)	5.84 (5.82)
II c	$C_{15}H_{10}FN$	96-98	76	80.70 (80.68)	4.51 (4.49)	6.27 (6.25)
II d	$C_{15}H_9 Br N_2O_2$	150-152	70	54.74 (52.72)	2.76 (2.74)	8.51 (8.49)
II e	$C_{16}H_{13}N$	156-158	78	87.64 (87.62)	5.98 (5.96)	6.39 (6.37)
II f	$C_{16}H_{13}NO$	126-128	64	81.68 (81.66)	5.57 (5.55)	5.95 (5.93)
II g	$C_{16}H_{12}FNO$	138-140	62	75.88 (75.86)	4.78 (4.76)	5.53 (5.51)

Table-2: Antitubercular activity data of the compounds II (a-g)

Compound	MIC values (µg/ ml) *M. tuberculosis* $H_{37}Rv$
II a	100
II b	25
II c	>100
II d	>100
II e	25
II f	100
II g	50
Isoniazid	0.25

The results of the antitubercular activity screening show that Compounds II b, II e and II g showed significant antitubercular activity compared with the standard drug isoniazid. Table-2 reveals antitubercular activity (MIC) data for all the synthesized compounds.

CONCLUSION

In this research work we accomplished the synthesis of some novel series of 2-phenyl quinoline derivatives. The *in-vitro* antitubercular activity screening result of these compounds depicted them as promising antitubercular leads exhibiting good activity. Further enhancement in the activity can be achieved by slight modifications in the ring substituent.

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