Microwave assisted synthesis, characterization and anti-tubercular activity of 7-chloro-(4-quinolylhydrazone)

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Abstract: A series of 7-chloro-(4-quinolylhydrazone) derivatives was synthesized by reaction of 7-chloro-(4-quinolylhydrazine) and various substituted carboxaldehyde out of that most of the derivatives show significant antitubercular properties. The microwave assisted organic synthesis was applied to synthesize a series of 7-chloro-(4-quinolylhydrazone) derivatives. The characterizations of newly synthesized derivatives were done by modern analytical techniques like digital melting point apparatus, IR, NMR and mass spectroscopy.

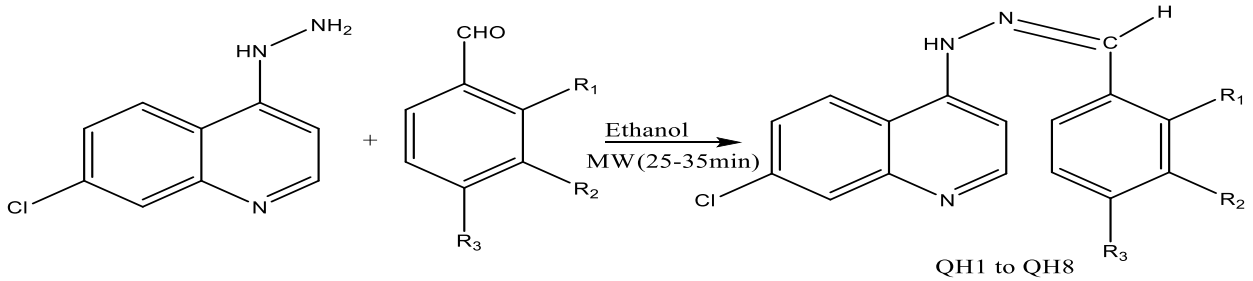
Keywords: Mycobacterium tuberculosis, Hydrazone, Quinoline, Carboxaldehyde.

INTRODUCTION

Tuberculosis (TB) is one of the most predominant infections in human beings and it has considerable contribution towards illness and death all around the world. Tuberculosis is caused by mycobacterium tuberculosis. (1) From previous research it is well known that quinolone is an important heterocyclic nucleus found in many natural as well as synthetic products having wide variety of pharmacological activities such as anti-TB (2), anticancer (3), antibacterial (4) and anti-inflammatory (5). The physicochemical study data of quinolone derivatives shows the potential antitubercular activity (6). During study of some 7-chloro-(4-quinolylhydrazone) derivatives exhibited significant activity (MIC=12.5-3.12 µg/ml) when compared to first line drugs such as ethambutol (MIC=3.12 µg/ml) (7). In reference to this in the search of new antituberculosis agents we proposed the synthesis of some quinolylhydrazones containing 7-chloro-(4-hydrazinylquinoline) moiety which was designed by molecular modeling (8). Because of its biological and synthetic versatility. From literature survey it is well known that quinolylhydrazone moiety are pharmacologically very active, they shows the activities like anti-inflammatory, antimicrobial and antitubercular (2). The latest development in the field of organic chemistry is the microwave assisted organic synthesis (MAOS) (9) (10) which provides short reaction time and economic use of reagents through green approach (11).

Chemistry: (For synthesis of QH1 to QH8)

The synthetic route for the preparation of 7-chloro-(4-quinolylhydrazone) derivatives QH1 to QH8 is summarized in scheme 1 as below.



Scheme 1: 7-chloro-(4-quinolylhydrazone), corresponding carboxaldehydes, Ethanol, Microwave (MW) 25-35 min

A Mixture of 7-chloro-(4-quinolylhydrazine) (1 equivalent), and carboxaldehyde (1 equivalent) in absolute ethanol was irradiated with temperature assisted microwave oven at 180W for 25-35 min with intermittence. All the Chemicals used are of AR grade from Merck, India. For completion of reaction it is monitored by TLC. After conformation of completion of reaction by TLC the reaction mixture is cooled and diluted with water, the respective hydrazones precipitated out from the reaction mixture. Which was purified with column chromatography by using ethyl acetate and n-hexane to yield expected hydrazone derivatives. The purified derivatives were recrystallized using suitable organic solvent. Furthermore, the characterizations of hydrazone derivatives were established on the basis of spectral data analysis.

The synthesized 7-chloro-(4-quinolylhydrazone) derivatives are subjected to in-silico (12) studies by Data warrior software for calculation of properties with their percentage yield, melting point, clogP and MIC value is summarized in table 1 as below.

Table: 1

Sr. No.	Hydrazones	Molecular Formula	Substitutions	% Yield	MP (ºC)	clogP[X]	MIC[Y] (µg/ml)
1	QH1	$C_{16}H_{12}ClN_3$	$R_1=R_2=R_3=H$	75	221-223	4.9802	9.52
2	QH2	$C_{16}H_{11}Cl_2N_3$	$R_3=Cl$, $R_1=R_2=H$	79	225-226	5.707	9.11
3	QH3	$C_{16}H_{11}ClN_4O_2$	$R_1=NO_2$, $R_2=R_3=H$	83	248-250	4.3858	9.54
4	QH4	$C_{16}H_{11}ClN_4O_2$	$R_2= NO_2$, $R_1=R_3=H$	85	272-274	4.7556	8.36
5	QH5	$C_{16}H_{11}ClN_4O_2$	$R_3= NO_2$, $R_1=R_2=H$	91	214-216	4.7556	8.87
6	QH6	$C_{17}H_{14}ClN_3O$	$R_3=OCH_3$, $R_1=R_2=H$	86	246-248	5.2076	9.78
7	QH7	$C_{16}H_{12}ClN_3O$	$R_3=OH$, $R_1=R_2=H$	85	225-226	4.9492	9.69
8	QH8	$C_{17}H_{12}ClN_3O_2$	$R_3=COOH$, $R_1=R_2=H$	82	219-221	4.9489	10.45

X Calculated by Data worrior, Y Minimum Inhibitory Concentration

Spectral characterization of 7-chloro-(4-quinolylhydrazone) derivatives:

(Z)-2-benzylidene-1-(7-chloroquinoline-4yl)hydrazine (QH1-$C_{16}H_{12}ClN_3$) (Mol. Wt. 281.74):

^{1}H NMR (DMSO, δ ppm, TMS) 8.13(s,1H),7.7(d,1H), 7.4(m,1H), 4.2(s,1H), 6.44(d,1H), 7.50(d,1H). ^{13}C NMR-145, 150.3, 134, 149,129.3, 128.9, 135.2, 125.8, 131.0. IR cm^{-1}- 3070(CH str), 1640(C=N str), 3320(NH str) MS m/z- 281.07(100%), 283.07(32.2%), 282.08(17.4%).

(Z)-2-(4-chlorobenzylidene)-1-(7-chloroquinoline-4yl)hydrazine (QH2-$C_{16}H_{11}Cl_2N_3$) (Mol. Wt. 316.18): ^{1}H NMR (DMSO, δ ppm, TMS) 8.12(s,1H),7.6(d,1H), 7.3(m,1H), 4.1(s,1H), 6.44(d,1H), 7.51(d,1H). ^{13}C NMR -143, 151, 136.1, 149.1, 128.6, 129.1, 135.3, 122.8, 132.0 IR cm^{-1} -3070(CH str), 1640(C=N str), 3320(NH str), 782(C-Cl) MS m/z-315(100%), 317(64.1%), 316 (17.4%).

(Z)-2-(2-nitrobenzylidene)-1-(7-chloroquinoline-4yl)hydrazine (QH3-$C_{16}H_{11}ClN_4O_2$) (Mol. Wt. 326.74):

^{1}H NMR (DMSO, δ ppm, TMS) 8.0(s,1H) 8.2(m,1H) 7.6(d,1H), 7.6(m,1H), 4.1(s,1H), 6.44(d,1H), 7.51(d,1H) . ^{13}C NMR -143, 148.2, 121, 132.1, 150, 139.2, 122, 127.2, 120.4 IR cm^{-1} -3070(CH str), 1640(C=N str), 3320(NH str), 1380(Ar-NO_2) MS m/z-326(100%), 328(32.07%), 327(17.5%).

(Z)-2-(3-nitrobenzylidene)-1-(7-chloroquinoline-4yl)hydrazine (QH4-$C_{16}H_{11}ClN_4O_2$) (Mol. Wt. 326.74):

^{1}H NMR (DMSO, δ ppm, TMS) 8.1(s,1H) 8.2(m,1H),8.5(s,1H) 7.6(d,1H), 7.6(m,1H), 4.1(s,1H), 6.46(d,1H), 7.51(d,1H). ^{13}C NMR -143, 148.2, 121, 132.1, 150, 139.2, 122, 127.2, 120.2, 113.4 IR cm^{-1} -3070(CH str), 1640(C=N str), 3320(NH str), 1421(Ar-NO_2 str) MS m/z-326(100%), 328(32.07%), 327(17.5%).

(Z)-2-(4-nitrobenzylidene)-1-(7chloroquinoline-4yl)hydrazine (QH5-$C_{16}H_{11}ClN_4O_2$) (Mol. Wt. 326.74):

^{1}H NMR (DMSO, δ ppm, TMS) 8.1(s,1H) 8.2(m,1H),8.7(s,1H) 7.6(d,1H), 7.6(m,1H), 4.1(s,1H), 6.46(d,1H), 7.51(d,1H), 7.43(d,1H). ^{13}C NMR -150.7,

143, 148.2, 121, 132.1, 149.2, 139.2, 122, 127.2, 119.8, 113.1 . IR cm^{-1} -3070(CH str), 1640(C=N str), 3320(NH str), 1489(Ar-NO_2 str) MS m/z-326(100%), 328(32.07%), 327(17.5%).

(Z)-2-(4-methoxybenzylidene)-1-(7-chloroquinoline-4yl)hydrazine (QH6-$C_{17}H_{14}ClN_3O$) (Mol. Wt. 311.77): ^{1}H NMR (DMSO, δ ppm, TMS) 8.1(s,1H) 8.2(m,1H), 8.65(d,1H) 7.6(d,1H), 7.6(m,1H), 4.1(s,1H), 6.46(d,1H), 7.51(d,1H), 7.43(d,1H). ^{13}C NMR -150.7, 143, 148.2, 121, 132.1, 149.2, 139.2, 122, 127.2, 119.8, 56.1, 113.3 IR cm^{-1} -3070(CH str), 1640(C=N str), 3320(NH str), 1266(Ar-$\underline{OCH_3}$) MS m/z-311(100%), 313(32.2%), 312(18.6%).

(Z)-2-(4-hydroxybenzylidene)-1-(7-chloroquinoline-4yl)hydrazine (QH7-$C_{16}H_{12}ClN_3O$) (Mol. Wt. 297.74):

^{1}H NMR (DMSO, δ ppm, TMS) 8.1(s,1H) 8.2(m,1H), 8.65(d,1H) 7.6(d,1H), 7.6(m,1H), 4.1(s,1H), 6.78(d,1H), 7.59(d,1H), 7.43(d,1H). ^{13}C NMR -160.6, 115.8, 143, 121, 125.5, 126.3, 130.3, 148.9 IR cm^{-1} -3070(CH str), 1640(C=N str), 3320(NH str), 1216(Ar-$\underline{OH}$) MS m/z-297(100%), 299(32%), 298(17.5%) .

(Z)-2-(4-formylbenzylidene)-1-(7-chloroquinoline-4yl)hydrazine (QH8-$C_{17}H_{12}ClN_3O_2$) (Mol. Wt. 325.75):

^{1}H NMR (DMSO, δ ppm, TMS) 11(s,1H) 8.1(s,1H) 8.2(m,1H), 8.64(d,1H) 7.6(d,1H), 7.6(m,1H), 4.1(s,1H), 6.78(d,1H), 7.59(d,1H), 7.43(d,1H). ^{13}C NMR-169.5, 130.1, 143, 121, 122.5, 127.3, 139.3, 148.9, 153.6 IR cm^{-1} -3070(CH str), 1640(C=N str), 3320(NH str), 1714(Ar-CO$\underline{OH}$) MS m/z-325(100%), 327(32.2%), 326(18.6%).

RESULTS AND DISCUSSION

The series of 7-Chloro-(4-quinolylhydrazone) derivatives from QH1 to QH8 had been synthesized using microwave assisted synthesis. Most of them show a good MIC value when compared with the first line drug Ethambutol with a very significant antitubercular activity. The analysis of hydrazone derivatives were carried out using melting point apparatus, the TLC plate used is coated with alumina, column chromatography on silica gel (60-120mesh) was applied when required. ^{1}H NMR spectra were recorded on VARIAN NMR spectrophotometer operating at 300MHz; TMS is used as internal standard. IR spectrum recorded on Shimadzu IRAffinity-1S and mass spectra were recorded using water Micromass Q-Tof Mic.

CONCLUSION

The series of novel antitubercular agents are synthesized and studied by very advanced and sophisticated instruments and low cost good quality chemicals. In this study it is observed that the hydrazone moiety having para substitution with withdrawing groups in benzylidene ring shows significant antitubercular activity studied by SAR study. In future this can be extended to synthesize more new derivatives and to study their practical application as potential antitubercular drugs.

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