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NOTE

2-Methyl 4-quinoline-hydrazide Derivatives as Antitubercular/ Antibacterial Agents—Part I

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Quinoline-hydrazide derivatives were synthesized and screened for their antibacterial and antitubercular activities.

A number of quinoline derivatives have been prepared recently and tested against microorganisms *viz. Escherichia coli*, *Salmonella paratyphi-B*, *Staphylococcus aureus* and *Mycobacterium tuberculosis* $H_{37}R_v$. The antitubercular effect at concentration of 5 μg/mL against $H_{37}R_v$ shows that such compounds have significance as anti-TB agents; however, there is no correlation between anti-tubercular and anti-bacterial activities. The substitutes —OCH_3, —OC_2H_5, —Cl and —CH_3 in quinoline nucleus enhance the anti-TB activity in general.[1]

In the present work at this research centre 4-chloro-2-methyl quinolines have been prepared by the known method and condensed with different hydrazides at —NH_2 group and at —NH of 8-chloro-4-methyl (1H)-2-quinolinone.[2]

All the chemicals used are either BDH or E. Merck and of AR grade.

Synthetic Scheme

Ethyl acetoacetate

+ Aryl amine
↓ Catalyst HCl
Ethyl-β-arylamine crotonate
↓ $Ac_2O + H_2SO_4$
4-Hydroxy-2-methyl quinoline
↓ $POCl_3$
4-Chloro-2-methyl quinoline
↓ Hydrazide NH_2 (4-Q-Cl^+) Solvent (B.P.)
2-Methyl-4-quinoline hydrazide

+ 2-Chloro aniline
↓ glacial acetic acid (B.P.)
2-Chloro aceto acetanilide
↓ Con. H_2SO_4 (90–100°C)
4-Methyl-8-chloro-2-quinolinone
↓↑
4-methyl-8-chloro-2-hydrxy quinoline
Reflux ↓ $POCl_3$
2,8-Dichloro-4-methyl quinoline
arylamine + 2,8-Q-Cl_2
↓ Solvent (B.P.)
Substituted iminophenyl 8-chloro-4-methyl quinoline or Hydrazides + 2, 8-Q-Cl_2
↓ Solvent (B.P.)
8-Chloro-4-methyl-2-quinolinyl-substituted hydrazides

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TABLE-1
PHYSICAL AND BIOLOGICAL ACTIVITY DATA OF SYNTHESIZED COMPOUNDS

Compound No.	Compound/(m.f.)	m.p. (°C)	Yield %	N % found	Antitubercular activity. $H_{37}R_v^*$	Antibacterial activity (5.0 µg/ mL) (Zones of inhibition in mm)		
					M. tuberculosis	*S. aureus*	*E. coli*	*S. paratyphi-B*
1.	2,6-Dimethyl-4-(O-2′,6′-dichloro phenyl aminophenyl acetyl hydrazino) quinoline ($C_{25}H_{22}N_4OCl_2$)	290	75.2	11.9	—	9.0	6.0	8.0
2.	2-Methyl-6-chloro-4-(O-2′,6′-dichlorophenyl aminophenyl acetyl hydrazino) quinoline ($C_{24}H_{19}N_4OCl_3$)	276	73.0	11.5	—	8.0	6.0	9.0
3.	2-Methyl-8-methoxy-4-[2′-(3″-trifluoromethyl phenyl amino)-3-pyridoyl hydrazino] quinoline ($C_{24}H_{20}N_5O_2F_3$)	274	83.5	14.8	—	9.0	6.0	8.0
4.	2,5-Dimethyl-4-(2′,3′:6′,7′-dibenzoazocin- 1′-yl carbonyl hydrazino) quinoline ($C_{26}H_{22}N_4O$)	216	54.1	13.6	—	8.0	6.0	6.0
5.	2-Methyl-6-methoxy-4-(3′-pyridoyl hydrazino) quinoline ($C_{17}H_{16}N_4O_2$)	290	60.0	18.0	—	7.0	12.0	9.0
6.	2-(3′-Chloro-4′-fluoro) phenyl amino-8-chloro-4-methyl quinoline ($C_{16}H_{11}N_2Cl_2F$)	276	62.3	8.6	—	6.0	6.0	9.0
7.	2-(3′-Trifluoromethane) phenyl amino-8-chloro-4-methyl quinoline ($C_{17}H_{12}N_2ClF_3$)	256	67.1	8.2	—	7.0	7.0	6.0
8.	2-(4′-Ethoxy) phenyl amino-8-chloro-4-methyl quinoline ($C_{18}H_{17}N_2OCl$)	206	62.7	8.9	—	7.0	6.0	6.0
9.	8-Chloro-4-methyl-2-(O-2′,6′-dichlorophenyl aminophenyl acetyl hydrazino) quinoline ($C_{24}H_{19}N_4OCl_3$)	286	61.8	11.5	—	8.0	6.0	6.0

*"—" = No growth.

The structures of substituted compounds were also confirmed by IR, NMR spectral studies and moleculat weight determination by non-aqueous titration method.[3]

(1) 2-Methyl-6-methoxy-4-[-2′-(3″-trifluoromethylphenylamino)-3′-pyridoyl hydrazino] quinoline. (compound No. 3).
NMR: δ 2.66 (—CH_3), 3.36 (H_2O present in DMSO), 3.96 (—OCH_3), 6.96–8.0 (Ar), 8.49–8.6 (—NH—NH), 8.3 (—NH)
IR: 1650 cm^{-1} ν(C=O), 3300–3250 cm^{-1} ν(—NH), 1340 cm^{-1} ν(C=N), 1170–1100 cm^{-1} ν(CF_3), 3040 cm^{-1} ν(CH_3), 2840 cm^{-1} ν(—OCH_3), 1610–1350 cm^{-1} (substitued quinoline ring)

(2) 2-(4′-Ethoxy) phenylamino-8-chloro-4-methyl quinoline. (compound No. 3).
NMR: δ 2.6 (—CH_3), 1.45 (—OCH_2CH_3-Triplet), 4.05 (—OCH_2CH_3-Quartet), 6.97–7.18 (Ar), 7.8 (—NH)
IR: 3080 cm^{-1} ν(—CH_3), 3250 cm^{-1} ν(—NH), 1350 cm^{-1} ν(C=N), 760 cm^{-1} ν(—Cl), 1610–1340 cm^{-1} (substituted quinoline ring), 2850 cm^{-1} ν(—OC_2H_5)

The anti-tubercular activity was tested agaist *Mycobacterium tuberculosis* $H_{37}R_v$ by the method developed at SPAN Research Centre and the antibacterial activity against *S. aureus*, *E. coli*, *Salmonella paratyphi-B* was determined by cylinder-cup method as described by Bryant.[4]

Substitution of —CF_3, —Cl, —OCH_3, —CH_3 (in 6 position) or —OC_2H_5 group appears to increase antitubercular activity of four unsubstituted hydrazides because of their presence in quinoline nucleus. Few of these compounds are effective against any two above mentioned bacterial species together (Table-1).

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