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Substituted 4-Methylquinolines as a New Class of Anti-Tuberculosis Agents†

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Abstract—We report synthesis and anti-tuberculosis activities of a series of novel ring-substituted quinolines. The most effective compound of the series **3d** (MIC = 6.25 μg/mL, *Mycobacterium tuberculosis H37Rv* strain) was synthesized in one step; thus is an attractive lead molecule for anti-tuberculosis drug development. The results of this study represent the discovery of ring-substituted 4-methylquinolines as new class of potential anti-tuberculosis agents.

Tuberculosis disease has staged a lethal comeback primarily because of resistance development by the causative organism, *Mycobacterium tuberculosis* against all major anti-tuberculosis drugs, and the rising incidence of immuno-suppressed situations (through cancer chemotherapy, AIDS infection and transplantation).[1] Approximately, 8 million people develop tuberculosis each year, and 2–3 million people die annually from the disease; 95% of which reside in developing countries.[2,3] According to the World Health Organization (WHO) predictions, tuberculosis if unchecked, will claim more than 30 million lives over the next decade and infect another 90 million.[4–6] Furthermore, it is a well known fact that no tuberculosis specific drug has been discovered in the last 40 years. The inadequate armory of drugs in widespread use for the treatment, development of drug-resistant forms of the disease against most commonly used mainstay drug isoniazid, and lack of affordable new drugs are the limiting factors in fight against tuberculosis. Hence, there are unmet medical needs for novel, efficacious therapies that minimize resistance problems in *M. tuberculosis*. This underscores the continuing urgent need for the discovery of new structural classes of anti-tuberculosis agents to replace and/or to supplement the current drug regimens. To pursue this goal, our research efforts are directed towards discovery of new chemical entities and to optimize the structure to display the potent efficacy.

In continuing our drug discovery program, this preliminary communication describes the synthesis and hitherto unknown in vitro anti-*Mycobacterium tuberculosis* activities of novel ring-substituted 4-methylquinolines.

The mono and disubstituted 4-methylquinolines **2** and **3** represented in Scheme 1 have been synthesized in one step by reacting commercially available 4-methylquinoline (**1**) with various alkylcarboxylic acids in 10% sulfuric acid in the presence of ammonium persulfate and catalytic amounts of silver nitrate at 70 °C for 10 min. As reported by us earlier,[7–9] the reaction proceeds via silver catalyzed free radical oxidative decarboxylation of alkylcarboxylic acids by ammonium persulfate in 10% sulfuric acid as solvent.[10] Overall yields range from 25–90%, though not surprisingly lower yields and only formation of the monosubstituted cyclopropyl adduct (**2f**)[12] was observed (Table 1). Presumably, this is a consequence of competitive degradation of the cyclopropyl radical verses oxidative decomposition of the quinoline ring. On the other hand, the reduced yields were first observed for the adamantyl product (**2g**),[13] that may be attributed to the lower solubility of 1-adamantanecarboxylic acid in the aqueous reaction medium rather then steric factors. In this case, unlike the other alkylcarboxylic acids, a substantial quantity of 1-adamantanecarboxylic acid was found left unreacted in the reaction vessel at the conclusion of the reaction.

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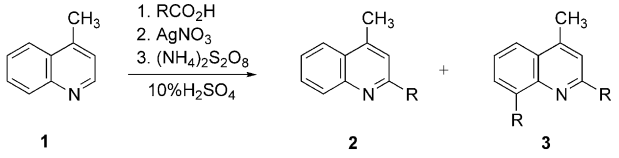

Scheme 1.

Table 1. Yields and antimycobacterial in vitro activity, expressed as MIC (μg/mL)[a], against *M. tuberculosis H37Rv* of ring-substituted 4-methylquinolines **2–3**

Compd	R	(%) Yield[b]	(%) Inhibition	MIC (μg/mL)
2a	$CH(CH_3)_2$	65	57	>6.25
2b[11]	$C(CH_3)_3$	75	ND[c]	ND
2c	*c*-C_4H_7	65	67	>6.25
2d	*c*-C_5H_9	70	74	>6.25
2e[11]	*c*-C_6H_{11}	65	16	>6.25
2f	*c*-C_3H_5	25	29	>6.25
2g	1-adamantyl	60	76	>6.25
2h	$(CH_2)_2CH_3$	45	30	>6.25
2i	$(CH_2)_3CH_3$	41	28	>6.25
2j	$(CH_2)_4CH_3$	35	24	>6.25
2k	$(CH_2)_5CH_3$	32	20	>6.25
3a	$CH(CH_3)_2$	22	71	>6.25
3b	$C(CH_3)_3$	21	ND	ND
3c	*c*-C_4H_7	25	100	12.5
3d	*c*-C_5H_9	24	100	6.25
3e	*c*-C_6H_{11}	23	53	>6.25
3h	$(CH_2)_2CH_3$	14	36	>6.25
3i	$(CH_2)_3CH_3$	12	33	6.25
3j	$(CH_2)_4CH_3$	14	29	>6.25
3k	$(CH_2)_5CH_3$	11	23	>6.25
1	H	—	0	>6.25

[a]MIC is defined as the lowest concentration inhibiting 90% of the inoculum relative to controls.
[b]Based on initial 4-methylquinoline.
[c]Not done.

However, the yield was improved to 60% through modification of the reaction conditions by first dissolving the 1-adamantanecarboxylic acid in acetonitrile, which was then added to the reaction mixture.[13]

All of the synthesized compounds **2** and **3** were evaluated for tuberculosis inhibition against *M. tuberculosis H37Rv* strain (ATCC 27294, susceptible both to rifampin and isoniazid) using the Microplate Alamar Blue Assay (MABA).[14] Compounds exhibiting fluorescence were then tested in the BACTEC 460 radiometric system[15] and results are summarized in Table 1. Compounds demonstrating at least 90% inhibition are re-tested at lower concentrations in the MABA and/or in BACTEC 460 radiometric assay to determine the actual Minimum Inhibitory Concentration (MIC), a value defined as the lowest concentration inhibiting 90% of the inoculum relative to controls.

Amongst the tested compounds, 4-methylquinoline analogue (**3d**) with two cyclopentyl groups placed at C-2 and C-8 position of the ring exhibited highest inhibitory activity (100%) at a concentration of 6.25 μg/mL (MIC). At the same time, 2,8-dicyclobutyl-4-methylquinoline (**3c**) also exhibited potent activity (100% inhibition) at a concentration of 12.5 μg/mL (MIC). Whereas, the monosubstituted counterparts of compounds **3c** and **3d** exhibited inhibitory activity (67 and 74%, respectively) that is far less efficacious compared to the disubstituted derivatives. Along the same lines, all other monosubstituted 4-methylquinoline analogues were found to be less effective (Table 1). Amongst the remaining disubstituted analogues, the diisopropyl derivative (**3a**) has shown inhibitory activity (71%) at >6.25 μg/mL; whereas, the dicyclohexyl derivative (**3e**) was found to be even less potent and has demonstrated only 63% inhibition at a concentration of >6.25 μg/mL. Interestingly, 4-methylquinoline (**1**), the starting material, utilized to prepare all analogues was completely devoid of any activity. These results indicates that placement of more than one cycloalkyl group containing maximum of five carbon atoms resulted in compounds with superior and enhanced biological activity. On the other hand, placement of a branched chain alkyl group at the quinoline ring led to derivatives with reduced anti-tuberculosis activity when compared to cycloalkyl derivatives. Finally, the placement of straight alkyl chain on the quinoline ring results in a further loss of anti-tuberculosis properties (Table 1).

The most effective compound (**3d**) of the series was also evaluated against *M. avium* complex (ATCC 25291, a strain susceptible to clarithromycin) and was found to be inactive at the initial tested concentration of 6.25 μg/mL. The same compound (**3d**) was further evaluated in vitro for cytotoxicity (IC_{50}) in VERO cells, along with safety index (SI) calculated as the ratio of IC_{50}/MIC_{H37Rv}, and results are reported in Table 2. Concurrently with testing of 2,8-dicyclopentyl-4-methylquinoline (**3d**) in *M. avium*, evaluation of activity against single-drug-resistant (SDR) *M. tuberculosis* was performed. The compound has shown good activity with MIC value of 12.5 μg/mL against rifampin (RMP-R), ethambutol (EMB-R), ciprofloxacin (CIP-R), and isoniazid (INH-R) resistant *M. tuberculosis* strains; whereas, it has exhibited moderate activity against kanamycin (KM-R) resistant strains with MIC value of 25 μg/mL (Table 2).

The minimum bactericidal concentration (MBC) for 2,8-dicyclopentyl-4-methylquinoline (**3d**) was then determined against *M. tuberculosis H37Rv* strain and against drug-resistant strain of isoniszid (INH-R) and rifampin (RMP-R) by subculturing onto drug-free solid media and enumerating colony forming units following exposure in supplemented Middlebrook 7H9 media to various concentrations of test compound. The observed minimum bactericidal concentrations (Table 3), which

Table 2. Cytotoxicity and SDR anti-tuberculosis activities of 2,8-dicyclopentyl-4-methylquinoline (**3d**)

No.	IC_{50} (μg/mL)	SI	Assay	Strain	MIC (μg/mL)
3d	>50	>8	Alamar	Erdman	50
			Alamar	EMB-R	12.5
			Alamar	RMP-R	12.5
			Alamar	CIP-R	12.5
			Alamar	KM-R	25
			Alamar	INH-R	12.5

Table 3. Minimum bactericidal concentration (MBC) assay data of 2,8-dicyclopentyl-4-methylquinoline (**3d**)

No.	Assay	MIC (*H37Rv*) (μg/mL)	Strain	MBC (μg/mL)	MBC/MIC (μg/mL)
3d	Alamar	25	H37Rv	50	2
			RMP-R	200	8
			INH-R	100	4

are higher, compared to MIC value does indicates that compound **3d** is bacteriostatic in nature.

We have described the synthesis and anti-tuberculosis activities of ring-substituted 4-methylquinoline analogues. The most significant aspect of this research is the exhibition of potent anti-tuberculosis activities in the reported compounds, which are synthesized in single step from inexpensive commercially available 4-methylquinoline (lepidine) via a homolytic free radical alkylation in excellent yield. The above results clearly established the discovery of ring-substituted 4-methylquinolines as a new class of anti-tuberculosis agents, and therefore, these molecules are very attractive for further chemical and biological optimization. Efforts are currently underway towards further optimization of the lead molecules through the replacement of methyl group with other synthetically negotiable groups at the various positions of the quinoline ring. Although, the most effective compound **3d** of the series is bacteriostatic in nature, it can be concluded that this class of compounds certainly holds great prospects, and that further exploration in this field may lead to potent anti-tuberculosis agents.

Typical procedure for the synthesis of ring-substituted 4-methylquinolines

A freshly prepared solution of ammonium persulfate (3 mmol) in water (7 mL) was added drop wise to a preheated (70 °C) mixture of 4-methylquinoline (**1**, 1 mmol), silver nitrate (0.6 mmol) and cyclopentanecarboxylic acid (2.2 mmol) in 10% H_2SO_4 (10 mL) during 5 min. The heating source was then removed and reaction proceeded with evolution of carbon dioxide. After 10 min, reaction mixture was poured onto ice, and resulting mixture was made alkaline with addition of 30% NH_4OH. Extracted with dichloromethane (3×20 mL), and combined extracts were washed with NaCl solution (2×5 mL). Dried over Na_2SO_4 and solvent removed in vacuo to afford a mixture of mono and disubstituted products, which were readily separated by flash column chromatography [EtOAc–hexanes, 10:90] over silica gel (230–400 mesh) to provide **2d** and **3d** (Table 1).

Spectral data for 2-cyclopentyl-4-methylquinoline (2d). Yield: 70%, mp: 80–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.84 (m, 6H, 3×CH_2), 2.15 (m, 2H, CH_2), 2.68 (s, 3H, CH_3), 3.30 (m, 1H, CH), 7.17 (s, 1H, Ar–H), 7.49 (m, 1H, Ar–H), 7.66 (m, 1H, Ar–H), 7.93 (d, 1H, Ar–H, J = 8.5 Hz), 8.03 (d, 1H, Ar–H, J = 8.5 Hz); analysis for $C_{15}H_{17}N$ (211.1), calcd, C, 85.26; N, 8.11; N, 6.63; found, C, 85.22; H, 8.02; N, 6.57; CIMS (NH_3) m/z 212 (M + 1).

Spectral data for 2,8-dicyclopentyl-4-methylquinoline (3d). Yield: 24%; oil, ^{1}H NMR ($CDCl_3$) δ 2.04 (m, 16H, 8×CH_2), 2.64 (s, 3H, CH_3), 3.19 (m, 1H, CH), 3.31 (m, 1H, CH), 7.10 (s, 1H, Ar–H), 7.40 (m, 1H, Ar–H), 7.86 (m, 2H, Ar–H); analysis for $C_{20}H_{25}N$ (279.2), calcd, C, 85.97; H, 9.02; N, 5.01; found, C, 85.99; H, 9.12; N, 5.05; CIMS (NH_3) m/z 280 (M + 1).

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12. *Spectral data for 2-cyclopropyl-4-methylquinoline (2f)*: Yield: 25%; mp: 57–58 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (m, 4H, 2×CH_2), 2.19 (m, 1H, CH), 2.65 (s, 3H, CH_3), 7.0 (s, 1H, Ar–H), 7.44 (m, 1H, Ar–H), 7.63 (m, 1H, Ar–H), 7.93 (m, 2H, Ar–H); analysis for $C_{13}H_{13}N$ (183.1), calcd, C, 85.21; H, 7.15; N, 7.64, found, C, 85.52; N, 7.02; N, 7.48; CIMS (NH_3) m/z 184 (M + 1).
13. In this particular case, 1-adamantanecarboxylic acid (2 mmol) was dissolved in CH_3CN (2.5 mL) at 70 °C followed by the addition of 4-methylquinoline (**1**, 1 mmol), silver nitrate (0.6 mmol) and 10% H_2SO_4 (10 mL). A freshly prepared

solution of ammonium persulfate (3 mmol) in water (7 mL) was added drop wise to the pre-heated (70 °C) reaction mixture during 5 min, and reaction mixture was allowed to stir for another 10 min. The reaction was worked up as for the protocol of other carboxylic acids described earlier. *Spectral data for 2-adamantan-1-yl-4-methylquinoline (2g)*: Yield: 60%; mp: 114–115 °C; ^{1}H NMR ($CDCl_3$) δ 1.64 (m, 15H, 6×CH_2 and 3×CH), 2.69 (s, 3H, CH_3), 7.32 (s, 1H, 3-Ar–H), 7.48 (m, 1H, Ar-H), 7.64 (m, 1H, Ar–H), 7.93 (d, 1H, 5-Ar–H, J = 8.2 Hz), 8.06 (d, 1H, 8-Ar–H, J = 7.7 Hz); analysis for $C_{20}H_{23}N$ (277.2), calcd, C, 86.59; H, 8.36; N, 5.05, found, C, 86.55; N, 8.33; N, 5.01; EIMS m/z 277 (M^+).

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