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Synthesis and antitubercular evaluation of novel substituted aryl and thiophenyl tethered dihydro-6*H*-quinolin-5-ones

Srinivas Kantevari [a,*], Santhosh Reddy Patpi [a], Balasubramanian Sridhar [b], Perumal Yogeeswari [c], Dharmarajan Sriram [c]

[a] *Organic Chemistry Division-II, Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b] *Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[c] *Medicinal Chemistry and Antimycobacterial Research Laboratory, Pharmacy Group, Birla Institute of Technology & Science-Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad 500 078, India*

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ABSTRACT

A series of novel aryl and thiophenyl tethered dihydro-6*H*-quinolin-5-ones have been synthesized in very good yields through $CeCl_3{\cdot}7H_2O$–NaI catalyzed one-pot condensation of β-enaminones derived from the respective methyl ketones; 1,3-cyclohexanedione & 5,5-dimethyl-1,3-cyclohexanedione and ammonium acetate refluxing in 2-propanol. Dihydro-6*H*-quinolin-5-ones **3a–f** was further derivatized to the respective hydroxymethyl analogs using proline as an organocatalyst in aqueous media. Among the all 18 compounds screened for in vitro antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ (MTB), dihydro-6*H*-quinolin-5-ones **4e** and **4f** were found to be most active with MIC 3.13 μg/mL.

Tuberculosis is a chronic infectious disease caused mainly by *Mycobacterium tuberculosis* (MTB).[1] It claims over two million lives worldwide each year and dwells hidden in as many as two billion people. It is estimated that between 2005 and 2020, one billion people will be newly infected, over 125 million people will get sick and 30 million will die of tuberculosis if control is not further strengthened.[1–3] In addition, the evolution of its new virulent forms like multi drug resistant (MDR-TB) and extremely drug resistant (XDR-TB) has become a major threat to human kind.[2] Among HIV infected people, the resurgence of TB is alarming due to the development of pathogenic synergy.[2,3] The worsening situation has prompted the world health organization (WHO) to declare tuberculosis a global public health crisis.[3] All the above facts also stressed an urgent need for development of fast acting new antitubercular drugs with diverse and unique structural features.[4]

In recent years, the quinolinone nucleus has gained considerable attention among medicinal chemists.[5] It is a key unit in several synthetic and natural products possessing wide range of biological activities. Streptonigrin, Lavendamycin and Ascidiathiazones (Fig. 1) are among the few quinolinone based successful drug candidates in the treatment of various diseases.[6] Thiophene is also an emerging pharmacophoric unit to induce variable pharmacological activities.[11] For instance, thienoquinolones display antitumour activity,[7] while thieno pyrimidones possess analgesic and anti-inflammatory activities.[8] Our quest for obtaining biologically more potent antitubercular agents prompted us to synthesize new aryl and thiophene embodied nitrogen heterocycles with quinolinone

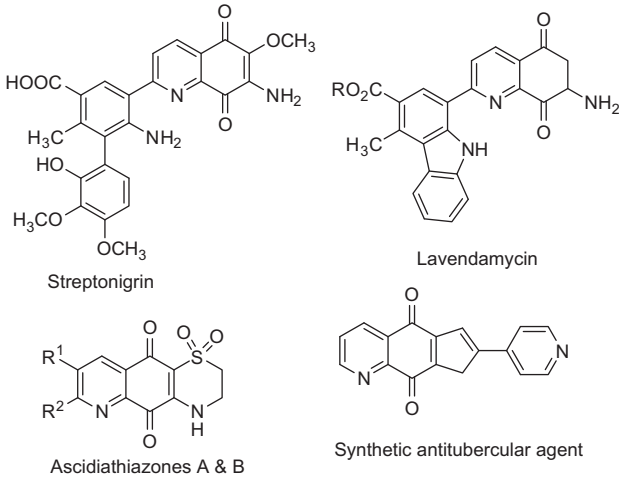

Figure 1. Representative bio-active quinolinones.

* Corresponding author. Tel.: +91 4027191437; fax: +91 4027198933.
E-mail addresses: kantevari@yahoo.com, kantevari@gmail.com (S. Kantevari).

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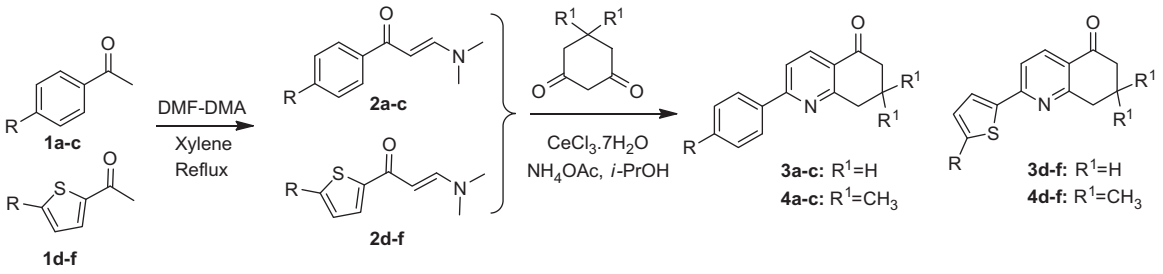


Scheme 1. Synthesis of dihydro-6*H*-quinoline-5-ones **3a–f** and **4a–f**.

Table 1
Synthesis of β-enaminones **2a–f**

S. no.	Ketone		β-Enaminone			Ref.
	1	R	**2**	Yield[a] (%)	mp (°C)	
1	**1a**	H	**2a**	90	87–88	10a
2	**1b**	CH_3	**2b**	86	90–91	10a
3	**1c**	OCH_3	**2c**	83	99	10a
4	**1d**	H	**2d**	88	101	11
5	**1e**	Cl	**2e**	82	106	–
6	**1f**	Br	**2f**	85.5	110	12

[a] Isolated yields.

backbone. We herein report an efficient synthesis of novel aryl and thiophenyl tethered dihydro-6*H*-quinolin-5-ones **3a–f**, **4a–f**, in excellent yields through $CeCl_3{\cdot}7H_2O$–NaI catalyzed one-pot condensation of β-enaminones (derived from aryl and thiophenyl methyl ketones **1a–f**), cyclic-1,3-dicarbonyls and ammonium acetate. The dihydro-6*H*-quinolin-5-ones **3a–f** were further derivatized to hydroxymethyl analogs **5a–f** using proline as an organocatalyst in aqueous media. Screening all new compounds **3a–f**, **4a–f** and **5a–f** for in vitro activity against *M.* tuberculosis $H_{37}Rv$ (MTB) resulted dihydro-6*H*-quinolin-5-ones **4e** and **4f** as most potent antitubercular agents with MIC of 3.13 μg/mL.

β-Enaminones,[9] being versatile substrates in the synthesis of heterocyclic compounds and drug intermediates, were chosen as starting material for the synthesis of dihydro-6*H*-quinolin-5-ones. They were prepared in excellent yields by the conversion of respective aryl and thiophenyl methyl ketones **1a–f** using dimethylformamide dimethylacetal refluxing in xylene (Scheme 1,Table 1). All β-enaminones **2a–f** formed from **1a–f** were fully characterized by ^1H and ^{13}C NMR, IR and mass spectral data.

On the basis of our recent work,[10] initially, β-enaminone **2a** was reacted with 5,5-dimethylcyclohexane-1,3-dione (dimedone) and ammonium acetate in the presence of 20 mol % of $CeCl_3{\cdot}7H_2O$–NaI catalyst (Scheme 1). The reaction was facile when $CeCl_3{\cdot}7H_2O$ in combination with NaI was used and no reaction took place with NaI alone. The reaction with $CeCl_3{\cdot}7H_2O$ alone requires 24 h to give product **4a** in 35% yield. Screening various solvents (DMF, methanol, 2-propanol, acetonitrile, water and neat) resulted optimum yield (89%) of target product **4a** in 2-propanol at reflux temperature. Having succeeded with the reaction, the enaminones **2a–f** in 2-propanol were refluxed with 1,3-cyclohexanedione or 5,5-dimethyl cyclohexane-1,3-dione and ammonium acetate in the presence of 20 mol % of $CeCl_3{\cdot}7H_2O$–NaI catalyst (Table 2). All the products **3a–f** and **4a–f** obtained in excellent yields (68–89%) were fully characterized by ^1H and ^{13}C NMR, IR and mass (ESI and HRMS) spectral data.

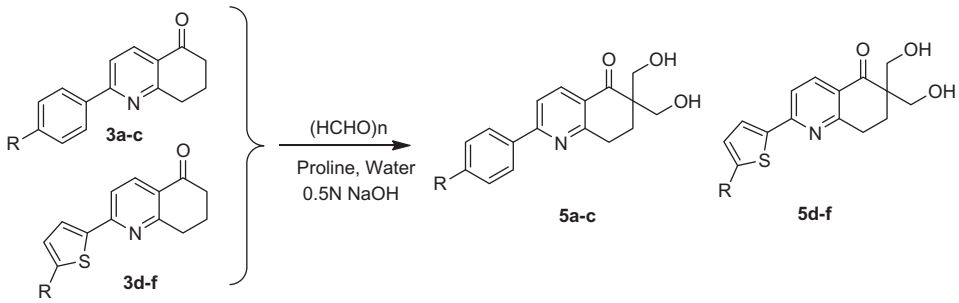
Further to obtain compounds with enhanced lipophobic nature, the dihydro-6*H*-quinolin-5-ones **3a–f** was subjected to hydroxymethylation at α-position to the carbonyl group. After series experiments, the reaction of dihydro-6*H*-quinolin-5-ones **3a–f** was successful with paraformadehyde in aqueous media using proline as an organocatalyst[12] under modified reaction conditions,[13] resulted products **5a–f** in very good yields (Scheme 2). The compounds **5a–f** was characterized[14] by ^1H and ^{13}C NMR, IR and mass (ESI and HRMS) spectral data. The single crystal X-ray diffraction studies of **5b** unambiguously confirmed structure (Fig. 2).

The antimycobacterial activity of the synthesized dihydroquinolinones **3a–f**, **4a–f** and **5a–f** has been screened in triplicate against *M. tuberculosis* $H_{37}Rv$ (MTB) by agar dilution method for

Table 2
Physical data and antitubercular evaluation of **3a–f** and **4a–f** against *M. tuberculosis* $H_{37}RV$

Entry	Enaminone **2**	Product			Yield[a] (%)	mp (°C)	Log *P*/*C* Log *P*[b]	MIC (μg/mL)
		R^1	R	**3**				
1	**2a**	H	H	**3a**	82	115	3.04/1.975	12.5
2	**2b**	H	CH_3	**3b**	80	88	3.52/3.621	12.5
3	**2c**	H	OCH_3	**3c**	76	96	2.91/3.140	12.5
4	**2d**	H	H	**3d**	73	98	3.02/3.014	12.5
5	**2e**	H	Cl	**3e**	70	116	3.39/3.748	6.25
6	**2f**	H	Br	**3f**	71	119	3.73/3.898	6.25
7	**2a**	CH_3	H	**4a**	89	67	3.84/3.013	12.5
8	**2b**	CH_3	CH_3	**4b**	85	119	4.32/4.659	6.25
9	**2c**	CH_3	OCH_3	**4c**	80	126	3.71/4.179	12.5
10	**2d**	CH_3	H	**4d**	68	85	3.82/4.052	6.25
11	**2e**	CH_3	Cl	**4e**	75	96	4.19/4.786	3.13
12	**2f**	CH_3	Br	**4f**	72	114	4.53/4.936	3.13
13	Isoniazid	–	–	–	–	–	–	0.1
14	Ethambutol	–	–	–	–	–	–	3.13
15	Pyrazinamide	–	–	–	–	–	–	50.0

[a] Isolated yields.
[b] Calculated using Chemdraw Ultra 11.0.



Scheme 2. Proline catalyzed synthesis of **5a–f**.

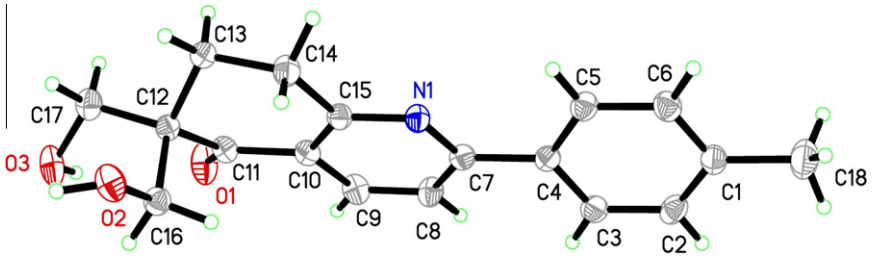


Figure 2. ORTEP representation of compound **5b** with thermal displacement ellipsoids drawn at the 30% probability.

Table 3
Physical data and antitubercular evaluation of **5a–f** against *M. tuberculosis* $H_{37}RV$

Entry	3	R	Product 5	Yield[a] (%)	mp (°C)	Log *P*/*C* Log *P*[b]	MIC (μg/mL)
1	**3a**	H	**5a**	50.6	130	2.19/0.950	>25.0
2	**3b**	CH_3	**5b**	66.7	156	2.67/2.597	>25.0
3	**3c**	OCH_3	**5c**	55.8	152	2.06/2.116	>25.0
4	**3d**	H	**5d**	68.2	147	2.17/1.990	>25.0
5	**3e**	Cl	**5e**	62.5	172	2.54/2.723	>25.0
6	**3f**	Br	**5f**	48.2	185	2.88/2.873	>25.0

[a] Isolated yields.
[b] Calculated using Chemdraw Ultra 11.0.

the determination of MIC. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. The MIC values of **3a–f**, **4a–f** and **5a–f** along with the standard drugs for comparison are furnished in Table 2 and 3. All the eighteen new compounds screened have shown in vitro activity against MTB with MIC ranging from 3.13 to 25.0 μg/mL. Four compounds **3e**, **3f**, **4b** and **4d** inhibited MTB with MIC of 6.25 μg/mL and two compounds **4e** and **4f** inhibited MTB with MIC of 3.13 μg/mL. When compared to one of the first line anti-TB drug ethambutol (MIC 3.13 μg/mL), two compounds **4e** and **4f** are found to be equally active as ethambutol. When compared to pyrazinamide (MIC 50.8 μg/mL), all the 18 compounds were found to be more potent, though all the compounds were less potent than another anti-TB drug isoniazid.

Structural correlations of the new compounds with respect to their antitubercular activity showed that introduction lipophobic hydroxymethyl groups (Scheme 2,Table 3) profoundly decreased their MIC values (>25 μg/mL). The result reveals that moderate lipophilic nature is needed for dihydro-6*H*-quinolin-5-ones to be active against *M. tuberculosis* $H_{37}Rv$ (MTB). In comparison with aryl tethered dihydro-6*H*-quinolin-5-ones, thiophenyl tethered dihydro-6*H*-quinolin-5-ones are better placed to show potent antitubercular activity (Table 2). Dihydro-6*H*-quinolin-5-ones derived from dimedone (entries 11 and 12, Table 2) are structurally better correlates and showed potent activity against *M. tuberculosis* $H_{37}Rv$ (MTB).

In conclusion, we have synthesized new aryl and thiophenyl tethered dihydro-6*H*-quinolin-5-ones in very good yields through $CeCl_3{\cdot}7H_2O$–NaI catalyzed one-pot condensation of β-enaminones, 1,3-cyclohexanedione & 5,5-dimethyl-1,3-cyclo hexanedione and ammonium acetate refluxing in 2-propanol. Proline catalyzed reaction of dihydro-6*H*-quinolin-5-ones **3a–f** with HCHO in aqueous media resulted hydroxymethyl analogs **5a–f** in good yields. Screening all these new derivatives against *M. tuberculosis* $H_{37}Rv$ (MTB) resulted dihydro-6*H*-quinolin-5-ones **4e** and **4f** as most potent antitubercular agents with MIC 3.13 μg/mL.

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14. *Representative spectral data*: *(E)-1-(5-Chlorothiophen-2-yl)-3-dimethylamin-opropenone (**2e**)* yield: 82%; mp: 106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 12.2 Hz, 1H), 7.34 (d, J = 3.9 Hz, 1H), 6.86 (d, J = 3.9 Hz, 1H), 5.43 (d, J = 12.2 Hz, 1H), 3.04 (d, br, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.67, 153.74, 146.12, 135.36, 127.42, 126.94, 90.59, 45.03, 43.73. IR (KBr) 2922, 2803, 1631, 1548, 1413, 1361, 1278, 1031, 881, 761 cm^{-1}. MS (ESI) m/z 216 $(M+H)^+$, 218 $(M+H+2)^+$; HRMS (ESI) calcd for $C_9H_{10}ClNOS$ $(M+H)^+$: 216.0249, found: 216.0257. *2-Thiophen-2-yl-7,8-dihydro-6H-quinolin-5-one (**3d**)* yield: 63.3%; mp: 90 °C. ^{1}H NMR ($CDCl_3$,100 MHz) δ 8.22 (d, J = 8.3 Hz, 1H), 7.65 (dd, J = 1.33 & 3.77 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.45 (dd, J = 1.33 & 5.09 Hz, 1H), 7.10 (dd, J = 3.77 & 5.09 Hz, 1H), 3.15 (t, J = 6.0 Hz, 2H), 2.66 (t, J = 6.0 Hz, 2H), 2.20 (qt, J = 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.4, 164.0, 155.5, 143.9, 135.6, 131.9, 129.7, 128.3, 126.5, 117.1, 38.4, 32.5, 21.7. IR (KBr) 3088, 2945, 1677, 1574, 1403, 1268, 1119, 833, 710 cm^{-1}. MS(ESI) m/z 230 $(M+H)^+$; HRMS (ESI) calcd for $C_{13}H_{11}NOS$ $(M+H)^+$: 230.0639, found: 230.0646. *7,7-Dimethyl-2-thiophen-2-yl-7,8-dihydro-6H-quinolin-5-one (**4d**)* yield: 73%; mp: 75 °C. ^{1}H NMR ($CDCl_3$,300 MHz) δ 8.2 (d, J = 8.1 Hz, 1H), 7.65 (dd, J = 1.3 Hz & 3.7 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.45 (dd, J = 1.3 Hz & 5.0 Hz, 1H), 7.11 (dd, J = 3.7 Hz & 5.0 Hz, 1H), 3.04 (s, 2H), 2.51(s, 2H), 1.15 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.5, 162.6, 156.0, 144.0, 135.2, 129.6, 128.3, 126.4, 125.2, 117.0, 52.0, 46.3, 32.9, 28.2. IR (KBr) 2943, 2865, 1683, 1573, 1402, 1294, 1108, 829, 717 cm^{-1}. MS(ESI) m/z 258 $(M+H)^+$; HRMS (ESI) calcd for $C_{15}H_{15}NOS$ $(M+H)^+$: 258.0952, found: 258.0947. 6,6-*Bis-hydroxymethyl-2-thiophen-2-yl-7,8-dihydro-6H-quinolin-5-one (**5d**)* yield: 68.2%; mp: 142 °C. ^{1}H NMR (DMSO, 300 MHz) δ 8.16 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 3.7 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 3.7 Hz, 1H), 7.12 (t, J = 3.7 Hz, 1H), 4.20 (br s, 2H), 3.80–3.65 (m, 4H), 3.20 (t, J = 6.4 Hz, 2H), 2.22 (t, J = 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.1, 162.8, 154.7, 143.5, 135.3, 131.2, 129.2, 128.0, 127.8, 126.0, 63.0, 51.7, 28.9, 27.8. IR (KBr) 3348, 2926, 1669, 1574, 1407, 1234, 1043, 945, 852, 727 cm^{-1}. MS(ESI) m/z 290 $(M+H)^+$; HRMS (ESI) calcd for $C_{15}H_{15}NO_3S$ $(M+H)^+$: 290.0850, found: 290.0846.