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Facile Diversity-Oriented Synthesis and Antitubercular Evaluation of Novel Aryl and Heteroaryl Tethered Pyridines and Dihydro-6*H*-quinolin-5-ones Derived via Variants of the Bohlmann−Rahtz Reaction

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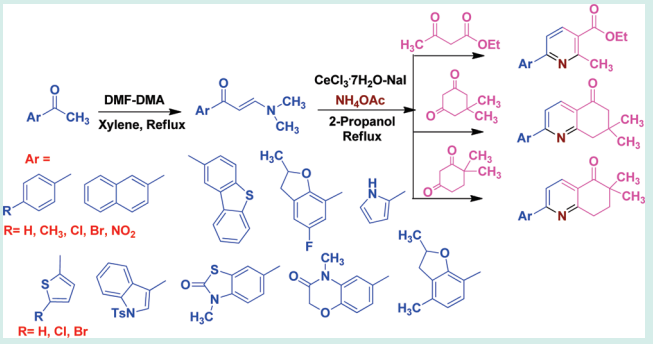
Supporting Information

ABSTRACT: The diversity oriented synthesis of substituted pyridines and dihydro-6*H*-quinolin-5-ones tethered with aryls and heteroaryls was achieved in very good yields through $CeCl_3 \cdot 7H_2O$-NaI catalyst via variants of the Bohlmann−Rahtz reaction. β-Enaminones derived from various aryl and heteroaryl methyl ketones were regioselectively reacted with ethyl acetoacetate or 5,5-dimethylcyclohexane-1,3-dione or 4,4-dimethylcyclohexane-1,3-dione and ammonium acetate refluxing in 2-propanol. Applicability of nontoxic cerium catalyst, high reactivity with wide range of aryl and heteroaryl β-enaminones leading to diverse analogues, operational simplicity, and shorter reaction time at comparatively low temperatures are prominent features of the developed protocol. These synthesized substituted pyridines and dihydro-6*H*-quinolin-5-one analogues have been evaluated for their in vitro antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB) by agar dilution method. Among the 48 compounds screened, six compounds 2-(5-chlorothiophen-2-yl)-7,7-dimethyl-7,8-dihydro-6*H*-quinolin-5-one **4**{*13,2*}, 2-(5-bromothiophen-2-yl)-7,7-dimethyl-7,8-dihydro-6*H*-quinolin-5-one **4**{*14,2*}, 2-(5-chloro thiophen-2-yl)-6,6-dimethyl-7,8-dihydroquinolin-5(6*H*)-one **4**{*13,3*}, and 2-(5-bromothiophen-2-yl)-6,6-dimethyl-7,8-dihydroquinolin-5(6*H*)-one **4**{*14,3*}, 7,7-dimethyl-2-(naphthalen-2-yl)-7,8-dihydroquinoline-5(6*H*)-one **4**{*6,2*}, 6,6-dimethyl-2-(naphthalen-2-yl)-7,8-di hydroquinolin-5(6*H*)-one **4**{*6,3*} resulted as the most promising antitubercular agents.



KEYWORDS: enaminones, cerium(III) chloride, pyridines, regioselectivity, Bohlmann−Rahtz reaction, dihydroquinolinones

INTRODUCTION

In the current era of chemical genomics, the rapid identification of small molecules having efficacy to perturb the functions of enzymes and receptors is a major challenge for understanding the complex biological events and hence diseases.[1] Research in this direction has shown a dramatic shift of focus from natural products to the combinatorial chemistry and diversity oriented synthesis (DOS).[2] In this contest, polysubstituted pyridines and dihydro-6*H*-quinolin-5-ones have gained considerable attention in recent years because of their broad spectrum biological activity. Notable among them are thiopeptide antibiotics, Streptonigrin, Lavendamycin (anti cancer), and MRZ-8676 (mGluR5 modulator) having substituted pyridine as central core unit (Figure 1).[3] With the exponential increase in potential therapeutic targets, a series of skeletal and stereochemical analogues have to be generated by using synthesis to meet demand on access to novel and diverse chemical libraries.[1,2] Therefore, numerous synthetic strategies for the preparation of these scaffolds have been developed. Among them, one-pot creation of 2,3,6-trisubstituted pyridines through the reaction of alkynones with 1,3-dicarbonyls under modified Bohlmann−Rahtz conditions is prominent one (Figure 2A).[4] Here, the functionalized alkynones and 1,3-dicarbonyls were custom synthesized and used as starting materials to annelate the trisubstituted pyridine system.[5] β-Enaminones, because of the presence of ambident nucleophilic character of enamine moiety and the ambident elctrophilic character of enone moiety, turned out to be simple synthetic intermediates[6] for the subject of the present synthesis (Figure 2B). Taking advantage of their electronic properties, we envisioned to use aryl and heteroaryl embodied β-enaminones as polarized

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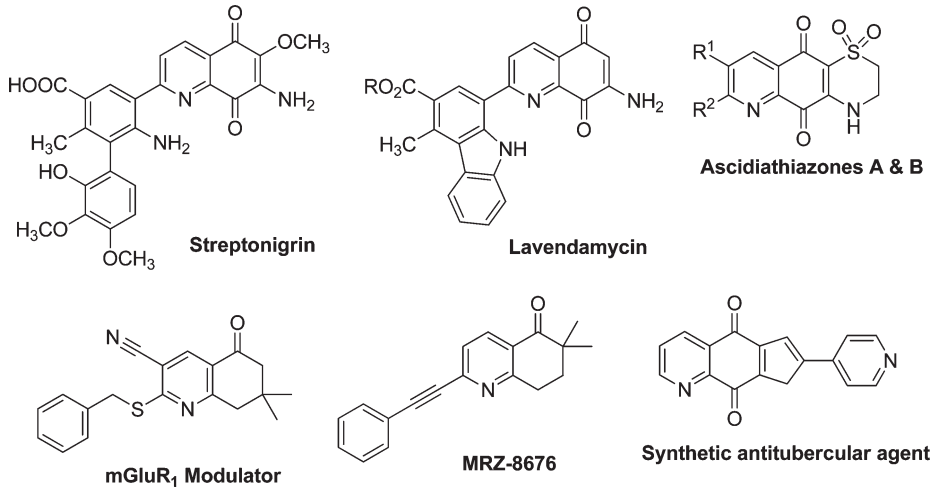

Figure 1. Representative bioactive quinolinone analogues.

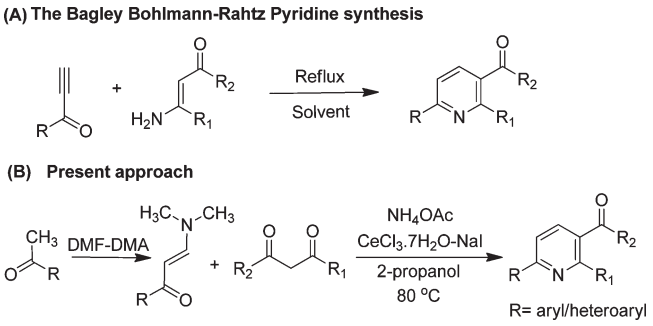

Figure 2. Approaches for the preparation of 2, 3, 6-trisubstituted pyridines.

variants of acetylenic ketones in the synthesis of 2,3,6-trisubstituted pyridines and quinolin-5-ones with three points of diversity.[7]

Synthesis of these substituted pyridines are reported by the reaction of β-enaminones with β-dicarbonyls in the presence of ammonium acetate in refluxing acetic acid, or by using Montmorillonite K10 in 2-propanol.[8] However, these methods suffer from low yields and exhibit limited substrate tolerance and reactivity. Recently, among the lanthanide catalysts, Cerium(III) chloride has emerged as a very cheap and efficient green reagent (in fact, it shows the same toxicity level as sodium chloride) and is able to catalyze various selective C−C bond forming reactions and cyclizations.[9] In most cases, the reactivity of $CeCl_3$ can be increased in combination with NaI.[9] The successful utility of Cerium(III) in reactions originated from 1,3-dicarbonyls[10] prompted us to investigate its applicability in one−pot condensation of various β-enaminones derived from aryl and heteroaryl methyl ketones with 1,3-dicarbonyls and ammonium acetate.

On the basis of our progressive endeavors in exploring novel one-pot reactions,[7] we herein report an efficient $CeCl_3 \cdot 7H_2O$-NaI catalyzed regioselective conversion of β-enaminones **1**{*1*−*16*} to novel substituted pyridines **3** {(*1*−*16*),*1*} and dihydro-6*H*-quinolin-5-ones **4**{(*1*−*16*),(*2*−*3*)} having appended aryl and heteroaryl groups through Michael addition, cyclodehydration and elimination sequence. One-pot reaction of substituted (*E*)-aryl and (*E*)-heteroaryl 3-(dimethylamino)-3-prop-2-enone **1**{*1*−*16*} (here after called as enaminones) derived from the respective commercially available aryl and heteroaryl methyl ketones; with readily available ethyl acetoacetate **2**{*1*} or cyclic 1,3-dicarbonyls **2**{*2*−*3*} and ammonium acetate in the presence of catalytic amount of $CeCl_3 \cdot 7H_2O$-NaI resulted title compounds with high regioselectivity at 2,3,6-positions. Furthermore the current method allows facile preparation of a library of novel substituted dihydroquinolin-5-ones for screening their biological activity. Among all the new compounds tested for in vitro antimycobacterial activity against *Mycobacterium tuberculosis H37Rv* (MTB), four compounds **4**{*13,2*}, **4**{*14,2*}, **4**{*13, 3*}, and **4**{*14, 3*} (MIC 3.13 μg/mL) and two compounds **4**{*6,2*} and **4**{*6, 3*} (MIC 1.56 μg/mL) resulted as the most active antitubercular agents.

RESULTS AND DISCUSSION

β-Enaminones **1**{*1*−*16*} (Figure 3) are generally prepared by the condensation of respective aryl and heteroaryl methyl ketones with dimethylformamide dimethylacetal (DMF-DMA) in refluxing xylene.[11]

Although the method is readily adopted, there is no synthetic protocol for the preparation of several β-enaminones used in this work. Literature described[11] β-enaminones were synthesized by a protocol standardized in our laboratory.[7] Extending it to other heteroaryl β-enaminones, (*E*)-1-(Dibenzo[*b,d*] thiophene-2-yl)-3-(dimethylamino)-2-propenone **1**{*7*}, (*E*)-3-Dimethyl amino-1-[1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]propenone **1**{*10*}, (*E*)-1-(5-Chlorothiophen-2-yl)-3-dimethylaminopropenone **1**{*13*}, (*E*)-6-(3-Dimethylaminoacryloyl-3-methyl-3*H*-benzothiazol-2-one **1**{*15*}, and (*E*)-6-(3-Dimethylamino acryloyl)-4-methyl-4*H*-benzo[*1,4*]xazin-3-one **1**{**16**} were synthesized in excellent yields. In case of **1**{*15*} and **1**{*16*}, methylation occurred at nitrogen prior to enaminone formation, and excess of DMF-DMA (4 equiv) was required to complete the conversion. All new as well as known enaminones **1**{*1*−*16*} were fully characterized by ^{1}H, ^{13}C NMR and mass spectral analysis. Further, the structure of enaminone **1**{*9*} was confirmed by single crystal X-ray analysis (Figure 4).

To affect the desired conversion of β-enaminones (polarized variant of Bohlmann−Rahtz substrate, alkynones) to substituted pyridines, we examined the three component reaction of

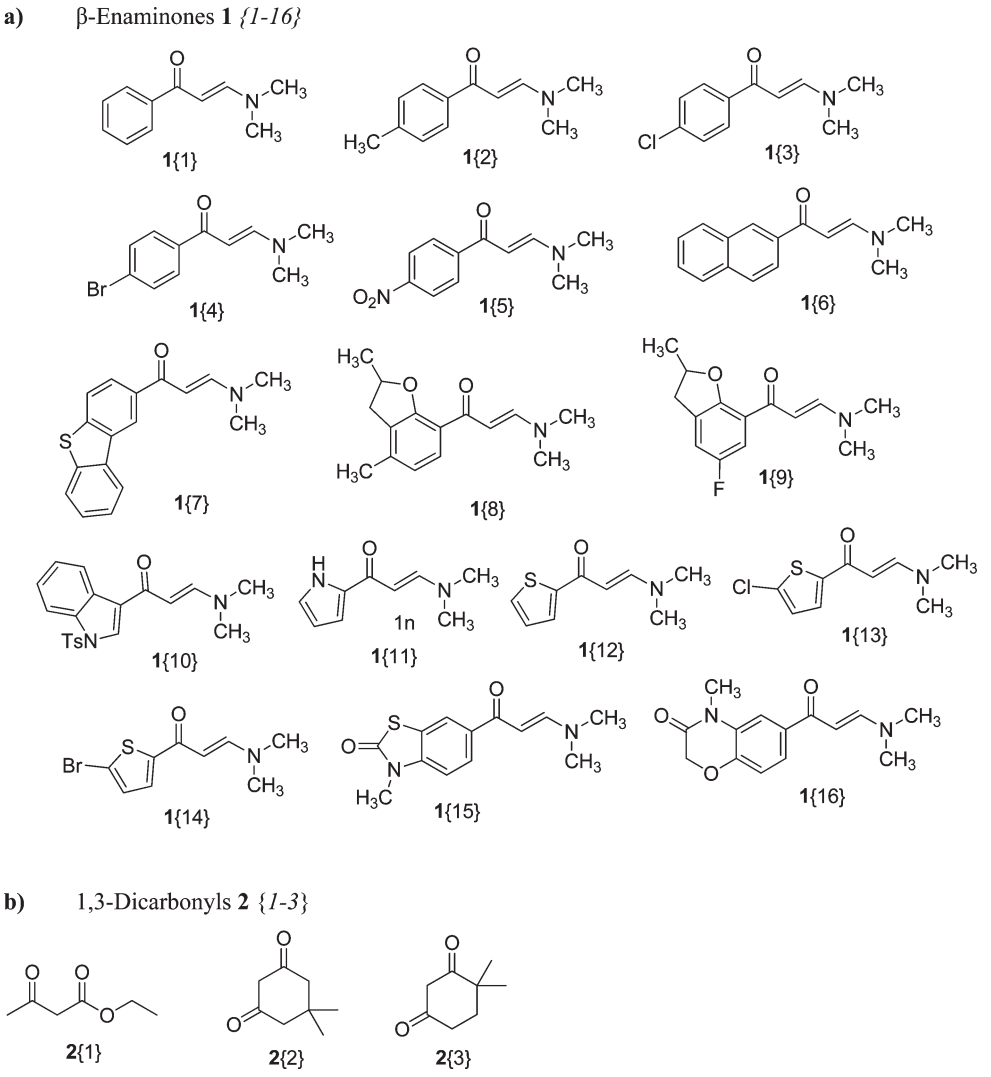

Figure 3. Diversity of reagents.

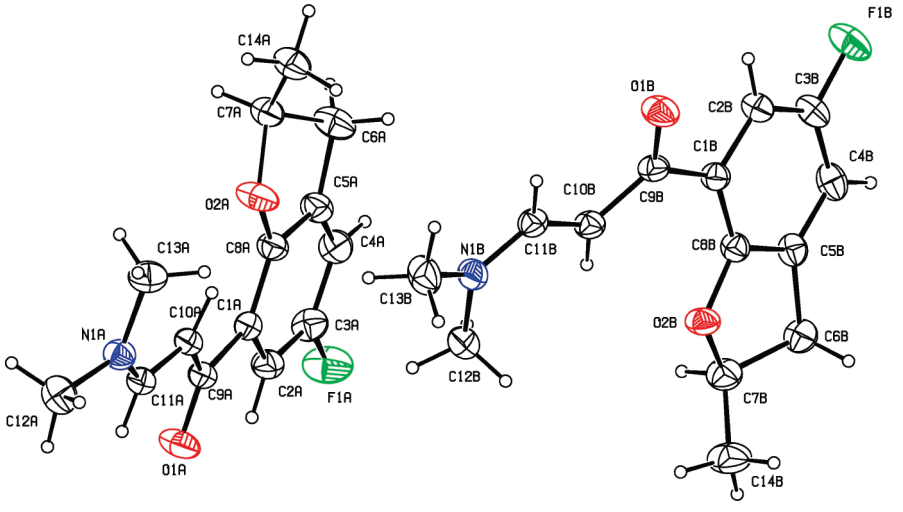

Figure 4. ORTEP diagrams of β-enaminone **1**{*9*} with thermal displacement ellipsoids drawn at the 30% probability level.

(*E*)-1-(thiophene-2-yl)-3-(dimethylamino)-2-propenone **1**{*12*}, ethyl acetoacetate **2**{*1*}, and ammonium acetate in the presence of different catalysts and reaction conditions. The results obtained are outlined in Table 1. The reaction was facile when

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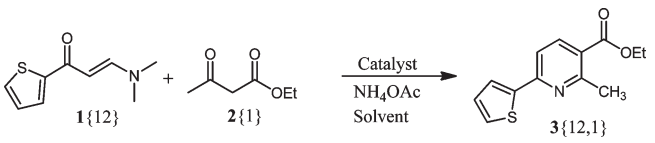
Table 1. Evaluation of Potential Catalysts[a]



entry	catalyst	mol %	time (h)	yield (%)[b]
1	AcOH		24	15.0
2	montmorilonite-K10	30	24	12
3	$K_5CoW_{12}O_{40}\cdot 3H_2O$	30	6	48.0
4	$Co(OAc)_2\cdot 4H_2O$	20	24	18.0
5	$CeCl_3\cdot 7H_2O$	20	24	32.0
6	$SnCl_2\cdot 2H_2O$	20	24	8.0
7	$Mg(ClO_4)_2$	20	24	13.0
8	$CeCl_3$ (Anhyd)	20	24	~3.0
9	$CeCl_3\cdot 7H_2O$-NaI	20	4.0	84.0
10	NaI	20	24	

[a] All the reactions were performed with **1**{12} (1.0 mmol), **2**{1} (1.2 mmol), and NH_4OAc (2.0 mmol) in the presence of catalyst, and the progress of the reaction was monitored by tlc. [b] Isolated yield.

$CeCl_3\cdot 7H_2O$ in combination with NaI was used, and no reaction took place with NaI alone. With $CeCl_3\cdot 7H_2O$ alone, the reaction requires 24 h to give **3**{*12, 1*} in 32% yield. Examining various solvents (DMF, methanol, 2-propanol, acetonitrile, water, and neat) resulted in optimum yield (84%) of target product **3**{*12, 1*} in 2-propanol at reflux temperature.

With optimal reaction conditions in hand, the generality of the protocol was explored (Table 2). A variety of structurally diverse β-enaminones **1**{*1*−*16*}, embodied with aryls and heteroaryls, were reacted with ethyl acetoacetate **2**{*1*} and ammonium acetate in the presence of $CeCl_3\cdot 7H_2O$-NaI in 2-propanol at reflux temperature. As illustrated in Table 2, all the β-enaminones **1**{*1*−*16*} were well tolerated to the reaction conditions and participated in the clean reactions with in 3.0 to 6.0 h, giving rise to the desired products **3**{*1*−*16,1*} in the yields ranging from 66% to 85%. All these substituted pyridine analogues **3**{*1*−*16,1*} were fully characterized by ^{1}H and ^{13}C NMR, IR and mass (ESI and HRMS) spectral data. Further, the structure of **3**{*9, 1*} was unambiguously confirmed by single crystal X-ray diffraction data (Figure 5).

To further examine the scope of this three component reaction, and to obtain more structurally diverse dihydro-6*H*-quinolin-5-ones, two readily available cyclic1,3-diones such as 5,5-dimethylcyclohexane-1,3-dione **2**{*2*} and 4,4-dimethylcyclohexane-1,3-dione **2**{*3*} were employed to react with all the aryl and heteroaryls embodied β-enaminones **1** {*1*−*16*} (Scheme 1, Table 3). As anticipated, the reaction of 5,5-dimethylcyclohexane-1,3-dione **2**{*2*} with all the β-enaminones **1** {*1*−*16*} and ammonium acetate were successful under the similar reaction conditions to give 2-substituted-7,7-dimethyl-7,8-dihydro-6*H*-quinolin-5-ones **4**{(*1*−*16*),*2*} in high yields (68% to 85%; Table 3). β-Enaminones **1**{*1*−*16*} were also reacted regioselectively with 4,4-dimethyl cyclohexane-1,3-dione **2**{*3*} and ammonium acetate under the similar reaction conditions to give 6,6-dimethyl-7,8-dihydroquinolin-5(6*H*)-ones **4**{(*1*−*16*),*3*} in very good yields (Table 3).

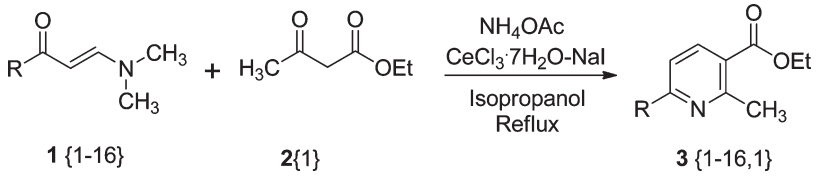
For example, the reaction of (*E*)-1-(5-Chlorothiophen-2-yl)-3-dimethylaminopropenone **1**{*13*}, 4,4-dimethylcyclohexane-1,3-dione **2**{*3*}, and ammonium acetate in the presence of $CeCl_3\cdot 7H_2O$-NaI in 2-propanol at reflux temperature gave exclusively 2-(5-chlorothiophen-2-yl)-6,6-dimethyl-7,8-dihydroquinolin-5(6*H*)-one **4** {*13,3*} in 65% yield. The formation of the other possible regioisomer **5** was not observed in all these reactions. The compound **4** {*13, 3*} was fully characterized by ^{1}H and ^{13}C NMR, IR, mass (ESI and HRMS) spectral data, and single crystal X-ray diffraction studies. The methylene protons of C7 and C8 in dihydroquinolinone moiety appeared as two triplets at δ 2.02 and 3.12, respectively. The regioselectivity of the gem dimethyl substituents at C6 position in dihydroquinolin-5(6*H*)-one **4** {*13, 3*} was unambiguously confirmed by single crystal X-ray studies (Figure 6).

Similarly, the regioselectivity in 6,6-dimethyl-2-*p*-tolyl-7,8-dihydroquinolin-5(6*H*)-one **4**{*2,3*} was also confirmed by single crystal X-ray analysis (Figure 7). The structures of all other 6,6-dimethyl-7,8-dihydroquinolin-5(6*H*)-ones **4**{(*1*−*16*),*3*} were also assigned using their ^{1}H and ^{13}C NMR, IR, mass (ESI and HRMS) spectral data. The observed regioselectivity for dihydroquinolin-5(6*H*)-ones **4**{(*1*−*16*), *3*} is due to their initial selective formation of 3-amino-6,6-dimethylcyclohex-2-enone **6** rather than 3-amino-4,4-dimethylcyclohex-2-enone **7** (Figure 8). A probable reason for the selectivity could be a steric effect. The conversion of carbonyl group to enamine would be through the formation of quaternary aminol **6A** and **7A**. The formation of **7A**, is less likely because the carbonyl adjacent to another quaternary carbon, the gem dimethyl, would be having significantly higher transition state energy trying to quaternize prior to dehydration. Such transition state energy might favors **6A** rather than **7A**.

All the synthesized substituted pyridines **3**{(*1*−*16*), *1*} and dihydro-6*H*-quinolin-5-one analogues **4**{(*1*−*16*), (*2*−*3*)} have been evaluated for their in vitro antimycobacterial activity against *M. tuberculosis* H37Rv (MTB) by the agar dilution method. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of the compound required to completely inhibit the bacterial growth. The determination of MIC values was performed in triplicate at pH 7.40. The MICs of the synthesized compounds **3**{(*1*−*16*), *1*}, **4**{(*1*−*16*), (*2*−*3*)} along with the standard drugs for comparison are depicted in Table 2 and 3. The LogP/CLogP values were calculated using Chembiodraw ultra 12.0.

All the 48 compounds screened have shown in vitro activity against MTB with MIC ranging from 1.56−25.0 μg/mL. When compared to one of the first line anti-TB drug ethambutol (MIC 3.13 μg/mL), four compounds **4**{*13,2*}, **4**{*14,2*}, **4**{*13, 3*}, and **4**{*14, 3*} (MIC 3.13 μg/mL) are found to be equally active as ethambutol, and two compounds **4**{*6,2*} and **4**{*6, 3*} (MIC 1.56 μg/mL) were found to be more potent than ethambutol. When compared to pyrazinamide (MIC 50.8 μg/mL), all the 48 compounds were found to be more potent, though all the compounds were less potent than the other anti-TB drugs isoniazid and Rifampicin (Table 2 and 3). Structural correlations of all the new compounds with respect to their antitubercular activity reveal that aryl and heteroaryl tethered 7,8-dihydroquinolin-5(6*H*)-ones **4**{(*1*−*16*),(*2*−*3*)} have shown better in vitro activity against MTB than the corresponding aryl and heteroaryl tethered pyridine derivatives **3**{(*1*−*16*), *1*}. All these results reveal that liphophilic nature along with halo substituents are needed for aryl and heteroaryl tethered 7,8-dihydroquinolin-5(6*H*)-ones **4**{(*1*−*16*), (*2*−*3*)} to become active against *M. tuberculosis* H37Rv (MTB). Among all the compounds evaluated, two compounds **4**{*6,2*} and **4**{*6,3*} (MIC 1.56 μg/mL) in which 7,8-dihydroquinolin-5(6*H*)-one tethered with naphthalene

Table 2. Synthesis, Physical Data, and Antitubercular Evaluation of 3{*1-16, 1*} against *M. tuberculosis* H37RV



1 {1-16} **2**{1} **3** {1-16,1}

entry	enaminone **1**{*1−16*}	react time (h)	product **3**	yield (%)[a]	m.p (°C)	LogP/CLogP[b]	MIC (μg/mL)
1	**1**{1}	4.0	**3**{*1,1*}	84	44	3.66/3.89	>25.0
2	**1**{2}	4.0	**3**{*2,1*}	80	54	4.15/4.39	>25.0
3	**1**{3}	4.5	**3**{*3,1*}	75	75	4.22/4.61	>25.0
4	**1**{*4*}	3.0	**3**{*4,1*}	86	73	4.49/4.76	25.0
5	**1**{*5*}	4.5	**3**{*5,1*}	74	142	2.96/3.64	25.0
6	**1**{*6*}	4.0	**3**{*6,1*}	85	98	4.66/5.06	6.25
7	**1**{*7*}	6.0	**3**{*7,1*}	68	86	5.69/6.30	25.0
8	**1**{*8*}	4.0	**3**{*8,1*}	82	96	4.32/5.06	25.0
9	**1**{*9*}	4.5	**3**{*9,1*}	80	60	3.99/4.78	6.25
10	**1**{*10*}	4.5	**3**{*10,1*}	76	102	5.19/6.21	25.0
11	**1**{*11*}	6.0	**3**{*11,1*}	66	55	2.20/2. 86	25.0
12	**1**{*12*}	4.0	**3**{*12,1*}	84	58	3.64/3.78	12.5
13	**1**{*13*}	4.5	**3**{*13,1*}	76	67	4.01/4.51	6.25
14	**1**{*14*}	4.0	**3**{*14,1*}	78	79	4.35/4.66	6.25
15	**1**{*15*}	6.0	**3**{*15,1*}	72	91	3.58/3.75	12.5
16	**1**{*16*}	6.0	**3**{*16,1*}	69	92	2.25/3.00	12.5
17	**Isoniazid**						0.1
18	**Ethambutol**						3.13
19	**Pyrazinamide**						50.8
20	**Rifampicin**						0.2

[a] Isolated yields. [b] Calculated using Chemdraw Ultra 12.0.

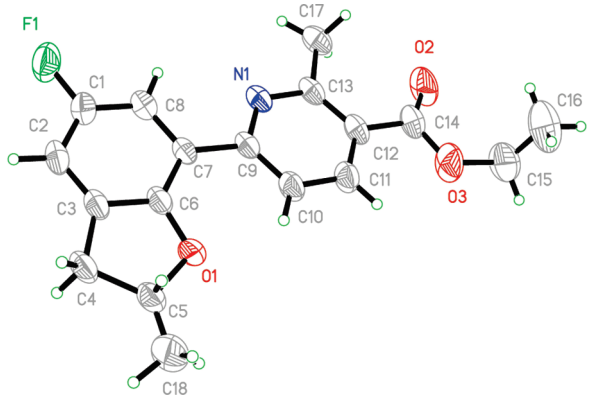


Figure 5. ORTEP diagrams of 3{*9,1*} with thermal displacement ellipsoids drawn at the 30% probability level.

resulted as the most active antitubercular agents against *M. tuberculosis* H37Rv (MTB).

CONCLUSION

In summary, we have accomplished a facile, diversity oriented synthesis of substituted pyridines 3{*1−16,1*} and dihydro-6*H*-quinolin-5-ones 4{(*1−16*), (*2−3*)} tethered with aryls and heteroaryls through $CeCl_3 \cdot 7H_2O$-NaI catalyst via variants of the Bohlmann−Rahtz reaction. Because of the presence of ambident nucleophilic character of the enamine moiety and the ambident elctrophilic character of the enone moiety, β-enaminones derived from various aryl and heteroaryl methyl ketones were efficiently used as polarized substrates in the reaction with ethyl acetoacetate or 5,5-dimethylcyclohexane-1,3-dione or 4,4-dimethylcyclohexane-1,3-dione and ammonium acetate refluxing in 2-propanol. The regioselectivity of dihydro-6*H*-quinolin-5-ones 4{*2,3*} and 4{*13,3*} accomplished in the reaction of β-enaminones with 4,4-dimethylcyclohexane-1,3-dione and ammonium acetate in the presence of $CeCl_3 \cdot 7H_2O$-NaI was assessed by single crystal X-ray crystallographic data. Applicability of nontoxic cerium catalyst, high reactivity with wide range of aryl and heteroaryl β-enaminones, operational simplicity, and shorter reaction time at comparatively low temperatures are prominent features of the developed protocol. Evaluation of the 48 compounds for their in vitro antimycobacterial activity against *M. tuberculosis* H37Rv (MTB) resulted in four compounds 4{*13,2*}, 4{*14,2*}, 4{*13, 3*}, and 4{*14, 3*} (MIC 3.13 μg/mL) and two compounds 4{*6,2*} and 4{*6,3*} (MIC 1.56 μg/mL) as most promising antitubercular agents.

EXPERIMENTAL SECTION

General Procedure for the Preparation of β-Enaminones 1{*1−16*}. To a solution of 6-acetyl-2*H*-1,4-benzoxazin-3(4*H*)-one

Scheme 1. Synthesis of Substituted Dihydroquinolin-5-ones 4{(*1*−*16*), (*2*−*3*)}

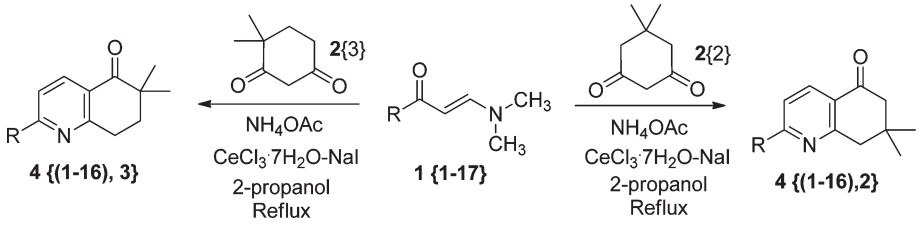


Table 3. Synthesis, Physical Data, And Antitubercular Evaluation of 4{*1*(*1-16*), *2*(*2-3*)} against *M. tuberculosis* $H_{37}RV$

entry	enaminone **1**{*1*−*16*}	dione**2**{*2*−*3*}	reaction time (h)	product **4**	yield (%)[a]	m.p (°C)	LogP/CLogP[b]	MIC (μg/mL)
1	**1**{*1*}	**2**{*2*}	4.0	**4**{*1, 2*}	78	67	3.84/4.16	>25.0
2	**1**{*2*}	**2**{*2*}	4.0	**4**{*2, 2*}	72	120	4.32/4.65	>25.0
3	**1**{*3*}	**2**{*2*}	4.5	**4**{*3, 2*}	82	105	4.39/4.88	12.5
4	**1**{*4*}	**2**{*2*}	3.0	**4**{*4, 2*}	85	132	4.67/5.03	12.5
5	**1**{*5*}	**2**{*2*}	4.5	**4**{*5, 2*}	76	182	3.41/3.91	>25.0
6	**1**{*6*}	**2**{*2*}	4.0	**4**{*6, 2*}	85	97	4.83/5.33	1.56
7	**1**{*7*}	**2**{*2*}	6.0	**4**{*7, 2*}	68	132	5.87/6.57	12.5
8	**1**{*8*}	**2**{*2*}	4.0	**4**{*8, 2*}	82	105	4.49/5.33	6.25
9	**1**{*9*}	**2**{*2*}	4.5	**4**{*9, 2*}	76	101	4.16/5.05	6.25
10	**1**{*10*}	**2**{*2*}	4.5	**4**{*10, 2*}	76	143	5.37/6.48	25.0
11	**1**{*11*}	**2**{*2*}	4.0	**4**{*11, 2*}	84	65	2.38/3.12	12.5
12	**1**{*12*}	**2**{*2*}	6.0	**4**{*12, 2*}	68	75	3.82/4.05	6.25
13	**1**{*13*}	**2**{*2*}	4.5	**4**{*13, 2*}	76	96	4.19/4.78	3.13
14	**1**{*14*}	**2**{*2*}	4.0	**4**{*14, 2*}	78	110	4.53/4.93	3.13
15	**1**{*15*}	**2**{*2*}	6.0	**4**{*15, 2*}	72	152	3.76/4.02	6.25
16	**1**{*16*}	**2**{*2*}	6.0	**4**{*16, 2*}	69	155	2.43/3.27	6.25
17	**1**{*1*}	**2**{*3*}	4.5	**4**{*1, 3*}	86	90	4.31/4.16	>25.0
18	**1**{*2*}	**2**{*3*}	4.0	**4**{*2, 3*}	84	104	4.80/4.65	>25.0
19	**1**{*3*}	**2**{*3*}	4.5	**4**{*3, 3*}	72	90	4.87/4.88	12.5
20	**1**{*4*}	**2**{*3*}	3.5	**4**{*4, 3*}	81	116	5.14/5.03	12.5
21	**1**{*5*}	**2**{*3*}	4.5	**4**{*5, 3*}	70	120	3.41/3.91	>25.0
22	**1**{*6*}	**2**{*3*}	4.0	**4**{*6, 3*}	73	80	5.31/5.33	1.56
23	**1**{*7*}	**2**{*3*}	5.0	**4**{*7, 3*}	65	142	6.34/6.57	12.5
24	**1**{*8*}	**2**{*3*}	4.0	**4**{*8, 3*}	76	97	4.97/5.33	12.5
25	**1**{*9*}	**2**{*3*}	4.0	**4**{*9, 3*}	72	106	4.64/5.05	6.25
26	**1**{*10*}	**2**{*3*}	4.5	**4**{*10, 3*}	70	132	5.84/6.48	>25
27	**1**{*11*}	**2**{*3*}	4.0	**4**{*11, 3*}	70	72	2.85/3.12	25.0
28	**1**{*12*}	**2**{*3*}	6.0	**4**{*12, 3*}	72	55	4.29/4.05	6.25
29	**1**{*13*}	**2**{*3*}	4.0	**4**{*13, 3*}	65	114	4.66/4.78	3.13
30	**1**{*14*}	**2**{*3*}	4.0	**4**{*14, 3*}	68	122	5.00/4.93	3.13
31	**1**{*15*}	**2**{*3*}	6.0	**4**{*15, 3*}	66	146	4.23/4.02	6.25
32	**1**{*16*}	**2**{*3*}	6.0	**4**{*16, 3*}	60	138	2.90/3.27	6.25
33	**Isoniazid**							0.1
34	**Ethambutol**							3.13
35	**Pyrazinamide**							50.8
36	**Rifampicin**							0.2

[a] Isolated yields. [b] Calculated using Chemdraw Ultra 12.0.

(1.0 g, 5.23 mmol) in xylene (15 mL) was added *N*,*N*-dimethylformamide dimethylacetal (2.91 mL, 20.92 mmol) and refluxed for 7 h (monitored by TLC). Xylene was then removed by distillation; crude residue was triturated with hexane. Solid residue thus formed was filtered to give (*E*)-6-(3-Dimethylaminoacryloyl)-4-methyl-4*H*-benzo[1,4]oxazin-3-one **1**{16} as a pure white solid (1.17 g, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, J = 12.2 Hz, 1H), 7.62 (d, J = 1.8 Hz, 1H), 7.48 (dd, J = 1.8 Hz and 8.3 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.64 (d, J = 12.2 Hz, 1H), 4.62 (s, 2H), 3.44 (s, 3H), 3.08 (d, br, 6H).

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^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.6, 164.0, 154.2, 147.3, 135.3, 129.2, 123.2, 120.1, 115.9, 114.5, 91.3, 67.4, 28.1. IR(KBr) 2919, 1685, 1635, 1545, 1355, 1238, 1121, 892, 766. MS(ESI) *m*/*z* 261 $(M+H)^+$; HRMS (ESI) Calcd for $C_{14}H_{16}N_2O_3$ $(M+H)^+$: 261.1239, found: 261.1230.

Synthesis of 6-(7,7-Dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-2-yl)-4-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (4{16,2}) As a Representative Example. To a mixture of (*E*)-6-(3-Dimethylaminoacryloyl)-4-methyl-4*H*-benzo[1,4]oxazin-3-one **1**{16} (0.27 g, 1.0 mmol), 1,3-cyclohexanedione **2**(*2*−*3*) (0.16 g, 1.2 mmol), ammonium acetate (0.15 g, 2.0 mmol) in 2-propanol (5 mL) were added $CeCl_3 \cdot 7H_2O$ (75 mg, 0.2 mmol), NaI (30 mg, 0.2 mmol) and refluxed for 4 h (monitored by TLC). The reaction mixture was cooled to room temperature; a solid precipitate was filtered and washed with cold 2-propanol. The combined solvent was evaporated, and the crude residue obtained was subjected to column chromatography (silica gel; hexane:ethyl acetate, 9:1) to obtain 6-(7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-2-yl)-4-methyl-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-one 4{*16,2*} (0.24 g, 69%) as pale yellow solid. mp 155 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.68−7.59 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 4.65 (s, 2H), 3.49 (s, 3H), 3.08 (s, 2H), 2.54 (s, 2H), 1.17 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.7, 164.1, 162.4, 159.8, 137.8, 135.4, 133.2, 129.9, 125.4, 123.0, 118.2, 117.0, 114.1, 67.5, 52.0, 46.7, 32.9, 29.6, 28.3, 28.1. IR(KBr) 2925, 2854, 1687, 1579, 1445, 1367, 1279, 1044, 831, 727 cm^{-1}. MS(ESI) *m*/*z* 337$(M+H)^+$; HRMS (ESI) Calcd for $C_{20}H_{21}N_2O_3$ $(M+H)^+$: 337.1552, found: 337.1569.

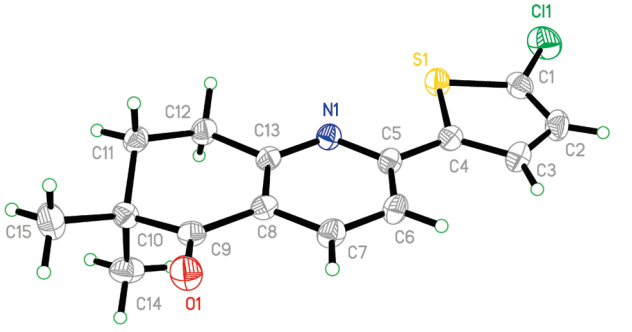

Figure 6. ORTEP diagram of 2-(5-chlorothiophen-2-yl)-6,6-dimethyl-7,8-dihydroquinolin-5(6*H*)-one **4** {*13, 3*} with thermal displacement ellipsoids drawn at the 30% probability level.

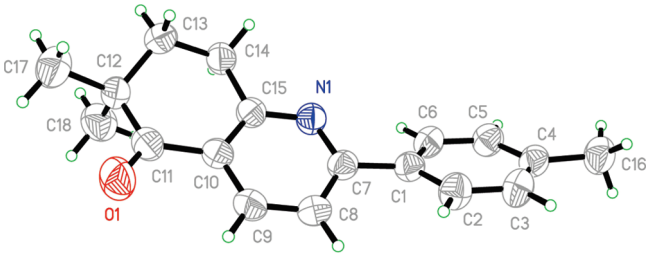

Figure 7. ORTEP diagram of 6,6-dimethyl-2-*p*-tolyl-7,8-dihydroquinolin-5(6*H*)-one **4**{*2,3*} with thermal displacement ellipsoids drawn at the 30% probability level.

General Procedure for in Vitro Antimycobacterial Evaluation of 3{(*1*−*16*), *1*} and 4{(*1*−*16*), (*2*−*3*)} Against *M. tuberculosis* H37Rv (MTB). Ten-fold serial dilutions of each test compound/drug were prepared and incorporated into Middle brook 7H11 agar medium with OADC Growth Supplement. Inoculum of *M. tuberculosis* H_{37}Rv ATCC 27294 (MTB) was prepared from fresh Middle brook 7H11 agar slants with OADC growth supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration approximately 10^7 cfu/mL. A 5 μL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated at 37 °C, and final readings were recorded after 28 days. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of test compound required to give complete inhibition of bacterial growth. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures for the synthesis of starting materials β-enaminones **1**{*1*−*16*}, Representative procedure for synthesis of pyridine derivatives **3**{(*1*−*16,1*}, dihydroquinolin-5-ones **4** {(*1*−*16*), (*2*−*3*)}; characterization data for all the products and copies of ^{1}H, ^{13}C NMR and mass (HRMS) spectra of all the new compounds; Single crystal X-ray diffraction data (cif files) for **1**{*9*}, **3**{(*9,1*}, **4** {*2,3*}, and **4** {*13,3*}. This material is available free of charge via the Internet at http://pubs.acs.org.

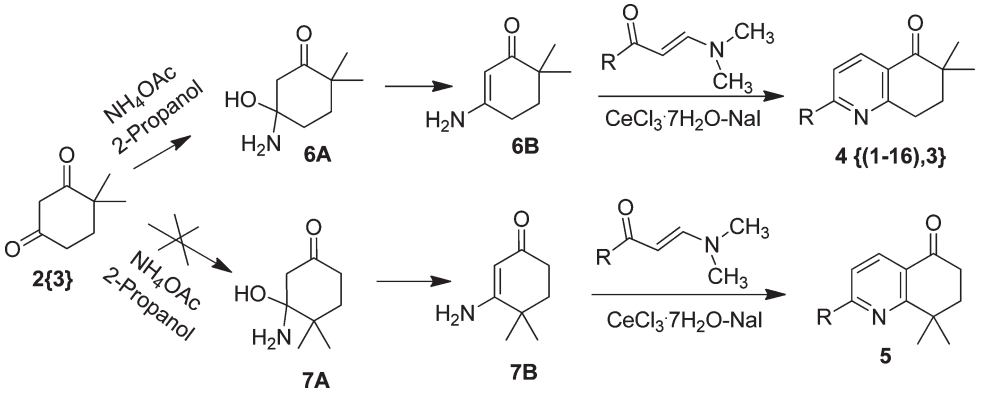

Figure 8. Regioselective formation of 6,6-dimethyl-7,8-dihydroquinolin-5(6*H*)-ones **4**{(*1*−*16*), *3*}.

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Author Contributions

S.K., S.R.P., D.A., and S.R.P. conceived, performed the experiments, and characterized the compounds with spectral data. B.S. performed single crystal X-ray analysis. P.Y. and D.S. evaluated compounds for antitubercular activity. S.K. and S.R.P. cowrote the manuscript and the Supporting Information.

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