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Synthesis and antimycobacterial activity of highly functionalized tetrahydro-4(1*H*)-pyridinones

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ABSTRACT

A series of 35 2e,3e,6e-triaryltetrahydro-4(1*H*)-pyridinones, 2e,3e,5e,6e-tetraaryltetrahydro-4(1*H*)-pyridinones and their *N*-nitroso and *N*-cyano analogs have been prepared. All these 35 compounds obtained were screened for their in vitro activity against *Mycobacterium tuberculosis* H37Rv (MTB). Among them, the *N*-nitrosopyridinones are found to be more active against MTB than the corresponding *N*-CN analogs, which, in turn, were slightly more active than NH analogs. In particular, the *N*-nitroso compounds, **3d**, **4b** and **4e** with halogen-bearing phenyl rings at 2,6-positions showed maximum activity with MIC values of 3.97, 3.11 and 3.11 μM, being more efficacious than the first line anti-TB drugs, ciprofloxacin, ethambutol and pyrazinamide. A general trend has also been discerned in all the three classes of NH, *N*-CN and *N*-NO compounds, in each of which those bearing four aryl rings display higher activity than that having three analogously substituted aryl rings disclosing that lipophilicity could be an important factor underlying antimycobacterial activity.

Tuberculosis (TB), a disease considered for long as substantially eradicated in developed countries, has resurged dramatically, establishing itself as one of the most dreaded infectious diseases resulting in the highest number of human deaths worldwide.[1–3] Approximately one-third of the world's population (~1.86 billion) is infected[4] with *Mycobacterium tuberculosis* (MTB). According to World health organization (WHO) estimates, there are about 8 million new active cases of TB, resulting in nearly 2 million deaths per year mostly from developing countries.[4,5] In addition, the number of people contracting TB is continuously on the rise, as their immune systems are impaired by immunosuppressive drugs, substance abuse and HIV. The contemporary treatment of TB involves administration of multi-drug regimen over a long period of time.[6,7] This leads to patient noncompliance and rapid emergence of multi-drug resistant and extensively drug resistant TB (MDR- and XDR-TB) strains, which impede the discovery and the development of new drugs.[8–10] In the last 50 years, only a few drugs have been approved by the Food and Drug Administration (FDA) for treating TB. This discloses the difficulties associated with the discovery and clinical testing of new agents and the lack of pharmaceutical industry research in this area.[11] Hence, the discovery of fast-acting effective new drugs possessing new mechanisms of action to cure TB is imperative.

Piperidones and their derivatives exhibit important biological activities such as anticancer,[12] anticonvulsant,[13] antiinflammatory[14] and local anaesthetic.[15] It is pertinent to note that in our recent studies, we have come across several heterocycles comprising piperidine rings displaying significant antimycobacterial activity.[16] In these studies, the nitrogen of the piperidine ring system as well as the groups attached to it are found to significantly contribute to and influence the activity. As the CN and NO groups linked to ring nitrogen could significantly alter the electron density of the ring nitrogen as well as the stereochemistry of piperidones, it was considered important from structure–activity point of view, to investigate the antimycobacterial activity of a library of NH, *N*-CN and *N*-NO-tetrahydro-4(1*H*)-pyridinones. Consequently, we have synthesized a library of thirty five highly functionalized NH, *N*-CN and *N*-NO-tetrahydro-4(1*H*)-pyridinones (Scheme 1), screened them for antimycobacterial activities in vitro against *M. tuberculosis* H37Rv (MTB) and report the results in this Letter. This work stems as a continuation of our recently embarked research on the synthesis of novel heterocycles and their screening against antimycobacterial activities.[16,17]

The 2e,3e,6e-triaryltetrahydro-4(1*H*)-pyridinones **1** and 2,3,5,6-tetraaryltetrahydro-4(1*H*)-pyridinones **2** were prepared by a literature method[18] and their *N*-nitroso derivatives **3** and **4**, respectively, were obtained by the reaction of **1** and **2** with sodium nitrite and hydrochloric acid in chloroform–water medium in good yields (Scheme 1, vide Supplementary data).

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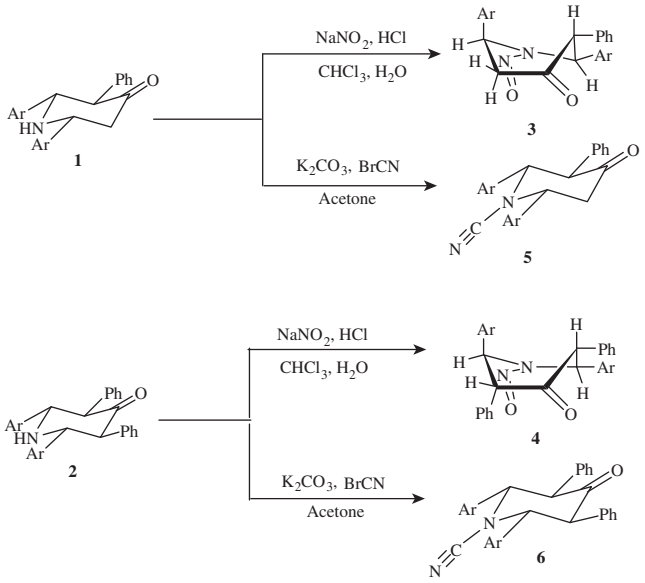

Scheme 1. Synthesis of tetrahydro-4(1*H*)-pyridinones **3**–**6**

The crystals of the pyridin-4-ones for X-ray crystallographic studies were obtained by recrystallization from ethanol–ethyl acetate mixture. In the case of unsymmetrical *N*-nitroso-2,3,6-triaryltetrahydro-4(1*H*)-pyridinones **3**, the partial double bond character of the *N*-NO functionality gives rise to two isomeric forms, *syn*- and *anti*-, and hence two sets of chemical shifts for the protons were obtained in NMR spectra. In solid state, these compounds adopt only one form as revealed by X-ray crystallographic study of **3c** (Fig. 1) which shows that the 2,6-bis(4-methylphenyl)-*N*-nitroso-3-phenyltetrahydro-4(1*H*)-pyridinone adopts a boat conformation.[19] The *N*-nitroso-2,3,5,6-tetraaryltetrahydro-4(1*H*)-pyridinones **4**, being symmetrical, give only one set of NMR signals. The X-ray crystallographic study of the compounds, viz., **4c**[20] (Fig. 2), **4d**[21] (Fig. 3), **4e**[22] (Fig. 4), **4f**[23] (Fig. 5), and **4g**[24] (Fig. 6) show that they all adopt a boat conformation in solid state.

Among the compounds **4c**–**4g**, **4e** and **4g** adopt a slightly twisted boat conformation, while the other compounds adopt almost a true boat form. The N-cyanation of **1** and **2** was carried out by reacting them with cyanogen bromide and potassium carbonate in acetone (vide Supplementary data), which afford the *N*-cyano-2e,3e,6e-triaryltetrahydro-4(1*H*)-pyridinones **5** and *N*-cyano-2e,3e,5e,6e-tetraaryltetra-hydro-4(1*H*)-pyridinones **6** (Scheme 1), respectively, in good yields. Both the *N*-cyanotri and tetraaryl compounds were found to exist in chair form as evident from the coupling constants of the vicinal protons of the heterocyclic rings in these compounds and from the X-ray crystallographic study of one representative compound **6a**[25] (Fig. 7).

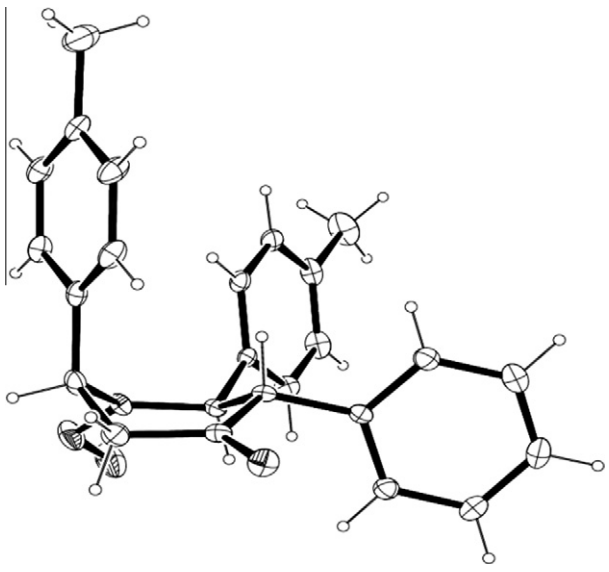

Figure 1. ORTEP diagram of **3c**.

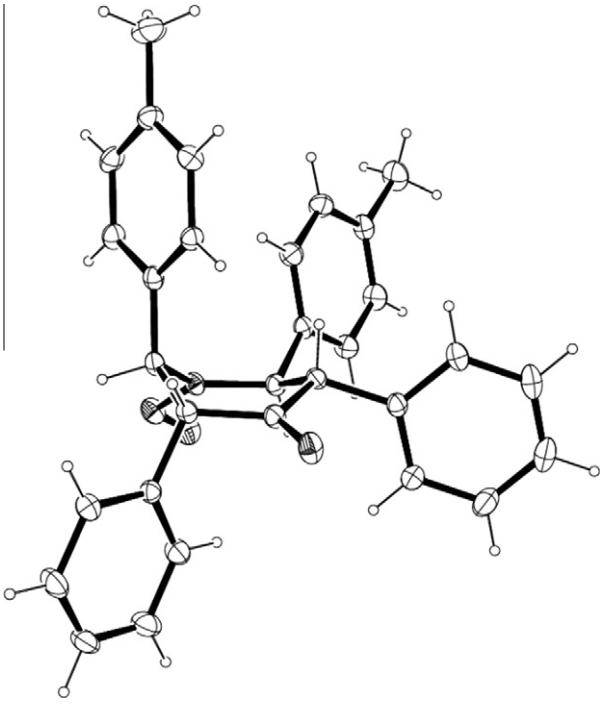

Figure 2. ORTEP diagram of **4c**.

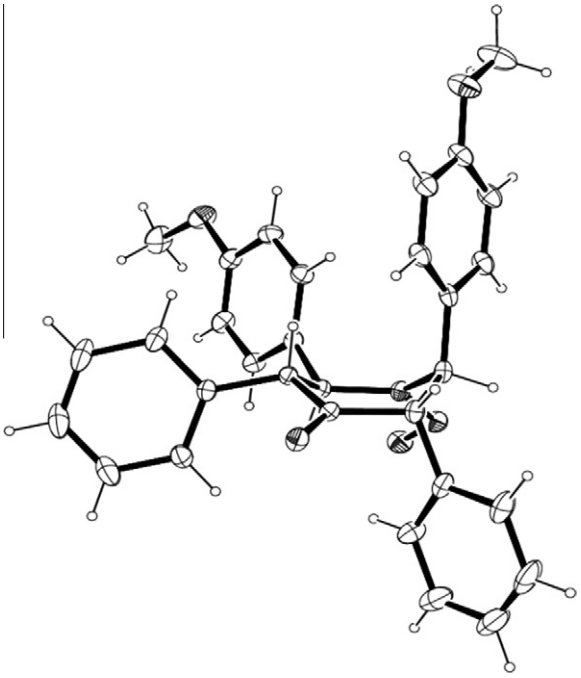

Figure 3. ORTEP diagram of **4d**.

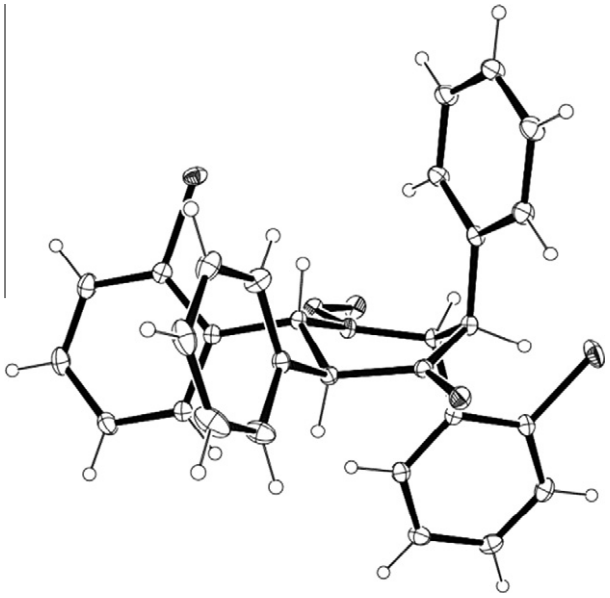

Figure 4. ORTEP diagram of **4e**.

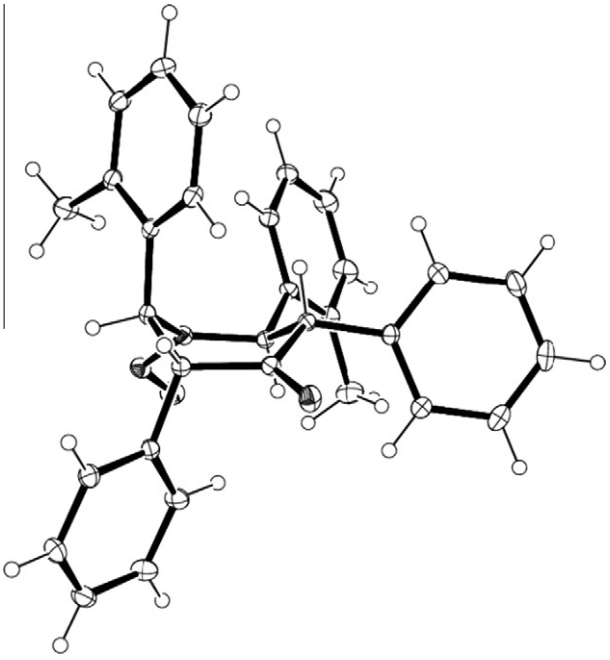

Figure 5. ORTEP diagram of **4f**.

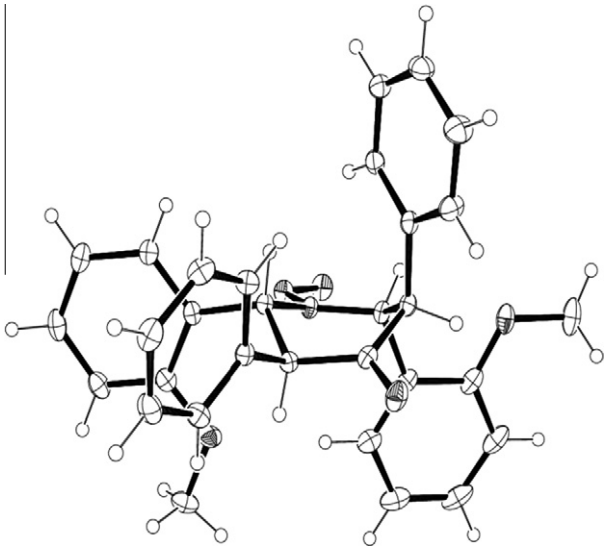

Figure 6. ORTEP diagram of **4g**.

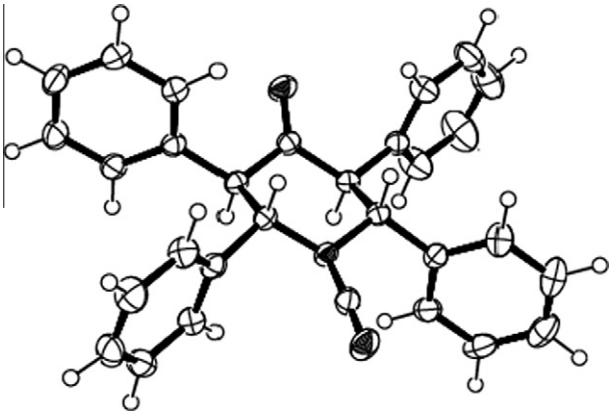

Figure 7. ORTEP diagram of **6a**.

The compounds **1a**–**6d** were screened for their in vitro antimycobacterial activity against MTB by agar dilution method for the determination of minimum inhibitory concentration (MIC) in duplicate at 7.40 pH. At this pH, the amine functionality of the compounds cannot be significantly protonated, and hence the free amine is responsible for the activity. The MIC is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. The MICs of the synthesized compounds along with that of the standard drugs for comparison are reported in Table 1 and Figure 8.

An examination of the data presented in Table 1 reveals that the NH-tetraaryltetrahydropyridinones **2** show higher activity than their triarylanalogs **1** bearing similarly substituted aryl rings at 2,6-positions. In a similar fashion, both *N*-nitroso and *N*-cyano compounds with four aryl rings possess higher activity than that of analogously substituted compounds bearing three aryl rings. These results suggest that lipophilicity could be an important contributory factor for activity. In both series **1** and **2**, compounds with halophenyl rings at 2,6-positions display enhanced efficacy against MTB as evident from MIC values of **1** having aryl rings with *p*-F (34.39 μM), *o*- and *p*-Cl (31.54 μM) and **2** having aryls with *p*-F (7.12 μM) and *o*- and *p*-Cl (13.23 μM). Among *N*-nitroso compounds **3** and **4** also, compounds with halogens in the aryl rings at 2,6-positions show greater efficacy against MTB as seen from MIC values of **3d** with *p*-flourophenyl rings (3.97 μM) and **4b** and **4e**, respectively, with *p*- and *o*-chlorophenyl rings (3.11 μM). Among the *N*-H (**1** and **2**), *N*-NO (**3** and **4**) and *N*-CN (**5** and **6**) compounds, the activity is found to be in the order: *N*-NO > *N*-CN > N-H disclosing that the N-substituent has a significant effect on the activity against MTB.

A comparison of the MIC values of all the compounds synthesized with that of the currently employed anti-TB drugs (Table 1 and Fig. 8) reveals that (i) 28 compounds have MIC values in the range 3.11–34.39 μM showing higher potency against MTB than the anti-TB drug pyrazinamide (MIC 50.8 μM), (ii) 8 compounds, viz., **2e**, **3b**, **3d**, **4b**, **4c**, **4e**, **4f** and **4g** have their MIC values falling in the range 3.11–7.35 with better activity than that of the drug ethambutol (MIC 7.6 μM), (iii) three compounds have their MIC

Table 1
Antimycobacterial activities of **1a–6d** against **MTB**.

Compound	Ar	MIC (μM)	Compound	Ar	MIC (μM)
1a[a]	4-ClC_6H_4	31.54	**3e**	2-MeC_6H_4	8.14
1b[a]	4-MeC_6H_4	70.32	**4a**[a]	C_6H_5	14.45
1c[a]	4-FC_6H_4	34.39	**4b**	4-ClC_6H_4	3.11
1d[a]	2-ClC_6H_4	31.54	**4c**	4-MeC_6H_4	6.79
1e[a]	2- MeC_6H_4	70.32	**4d**	4-$MeOC_6H_4$	12.68
1f[a]	2-$MeOC_6H_4$	64.52	**4e**	2-ClC_6H_4	3.11
2a[a]	C_6H_5	61.95	**4f**	2-MeC_6H_4	6.79
2b[a]	4-ClC_6H_4	13.23	**4g**	2-$MeOC_6H_4$	6.35
2c[a]	4-MeC_6H_4	28.96	**5a**	C_6H_5	70.93
2d[a]	4-$MeOC_6H_4$	26.96	**5b**	4-ClC_6H_4	29.66
2e[a]	4-FC_6H_4	7.12	**5c**	4-MeC_6H_4	65.70
2f[a]	2-ClC_6H_4	13.23	**5d**	4-$MeOC_6H_4$	30.30
2g[a]	2- MeC_6H_4	28.96	**5e**	4-FC_6H_4	16.09
2h[a]	2-$MeOC_6H_4$	26.96	**6a**	C_6H_5	58.33
3a[a]	C_6H_5	17.53	**6b**	4-ClC_6H_4	25.12
3b	4-ClC_6H_4	7.35	**6c**	2-ClC_6H_4	12.56
3c	4-MeC_6H_4	8.14	**6d**	2-MeC_6H_4	27.37
3d	4-FC_6H_4	3.97			
Isoniazid		0.4	Ethambutol		7.6
Ciprofloxacin		4.7	Pyrazinamide		50.8

[a] Known compounds.

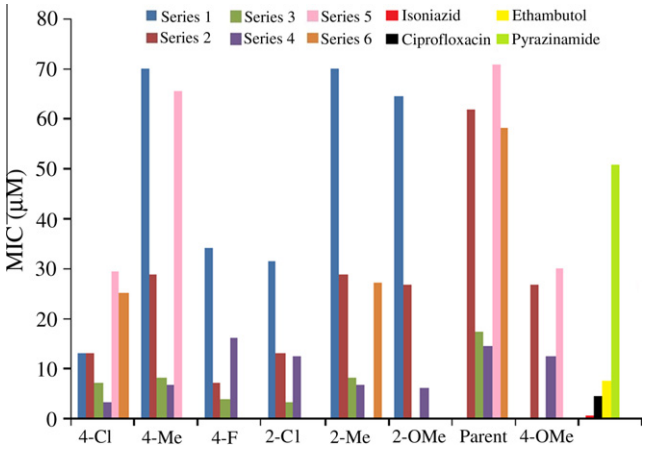

Figure 8. Antimycobacterial activity of **1–6** and standard drugs.

in the range 3.11–3.97 μM disclosing higher activity than the drug ciprofloxacin (MIC 4.7 μM) and all the compounds being less potent than isoniazid (MIC 0.4).

This work describes the synthesis and antimycobacterial screening of a library of 35 highly functionalized tetrahydro-4(1*H*)-pyridinones against *M. tuberculosis* H37Rv (MTB). The *N*-nitrosopyridinones display greater activity than the corresponding *N*-H and *N*-CN pyridinones. The presence of halogens in aryl rings enhances the activity rendering three compounds with higher potency than three standard anti-TB drugs, viz., ciprofloxacin, ethambutol and pyrazinamide.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.05.032.

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