2,4-Dinitroimidazole: Microwave Assisted Synthesis and Use in Synthesis of 2,3-Dihydro-6-nitroimidazo[2,1-*b*]oxazole Analogues with Antimycobacterial Activity

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2,4-Dinitroimidazole (2,4-DNI), an important starting material for nitroimidazooxazole and nitroimidazooxazine types of antitubercular agents was synthesized by rearrangement of 1,4-dinitroimidazole (1,4-DNI) under microwave irradiation. Various new nitroimidazooxazoles analogues were prepared using 2,4-DNI and were tested preliminarily against *Mycobacterium tuberculosis,* H_{37}Rv strain. Some were found to be active.

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Introduction.

Crystalline 2,4-dinitroimidazole (2,4-DNI) [1a-d] is an explosive, high-energy material. It is much less sensitive than RDX and HMX, and is about 15-20% more energetic than TATB [2]. It has both good thermal stability and impact insensitivity [1a]. It can be synthesized by refluxing 1,4-DNI in chlorobenzene [1d]. However, reaction is slow and requires more than 24 h (~50 hours) to give a yield of 80%. It can also be prepared in 63% yield by nitration of 2-nitroimidazole [3]. However, 2-nitroimidazole is not readily available. A process to convert 1,4-DNI into 2,4-DNI by direct melting is reported in a patent [1a], however, we were unable to reproduce this molten state rearrangement. The use of microwave is finding wide application in acceleration of many reactions [4a,4b]. We considered the possibility of acceleration of conversion of 1,4-DNI to 2,4-DNI under microwave irradiation and observed that the reaction was very fast, and within 2 min more than 70% conversion was observed. The proceedure gave reproducible results and is convenient to employ on a routine basis.

Apart from the high energetic value, 2,4-DNI is a very good radiosensitizing agent and also a valuable starting material for the synthesis of many potent chemotherapeutic agents [3,5a,5b]. Nitroimidazooxazoles [6] and nitroimidazooxazines [7] have also being well investigated for their antitubercular activity. CGI-17341 (**I**) and PA-824 (**II**) (Figure 1) are two of such agents that have exhibited potent activities against both active and latent tubercle bacilli. It is important to note that nitroimidazooxazoles and nitroimidazooxazines do not generate any cross-resistance [7] with antitubercular drugs such as INH, rifampin, streptomycin, ciprofloxacin, *etc*. Amongst a series of nitroimidazooxazoles possessing antimycobacterial activity, CGI-17341 (**I**) is the lead compound. Our preliminary efforts are directed towards the synthesis of newer potential analogues of bicyclic nitroimidazooxazole pharmacophore using 2,4-DNI as a starting material.

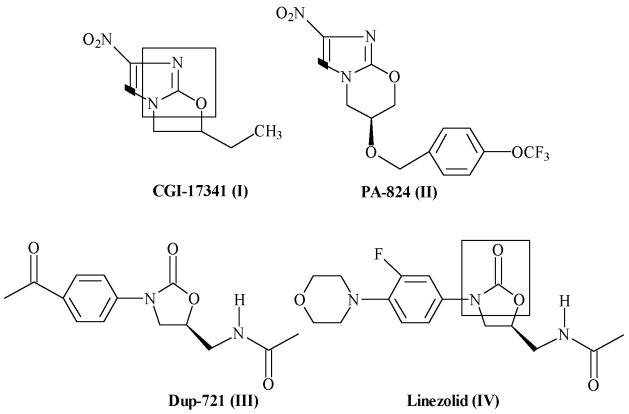


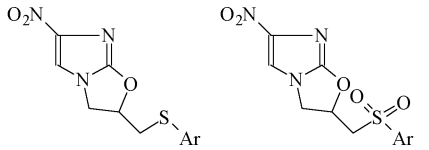
Figure 1. The chemical structures of CGI-17341(**I**), PA-824 (**II**), Dup-721(**III**) and Linezolid (**IV**).

The pharmacophore, bicyclic nitroimidazooxazole that is present in CGI-17341 (**I**) has close similarity with oxazolidinones like Dup-721 [8] and (**III**) Linezolid [9] (**IV**) (Figure 1) that are potent anti-bacterial agents against gram-positive bacteria. This encouraged us to synthesize newer analogues for anti-tubercular activity. Also random derivatization, and application of simple physicochemical principles across nitroimidazooxazole pharmacophore of CGI-17341 (**I**) may improve the understanding of structure activity relationships.

Chemistry.

An improved procedure for synthesis of 2,4-DNI **2** starting from 1,4-DNI **1** was developed using microwave irradiation. 2,4-DNI was efficiently prepared in a short time. All nitroimidazooxazole analogues were synthesized starting from 4-nitroimidazole [10] (Scheme 1). Reaction of 2,4-DNI with racemic epichlorohydrin generated a mixture containing three compounds [11]. The desired compound **3** was isolated by a solvent treatment and characterized. The aryl sulfide analogues **4** were prepared by reacting compound **3** with the corresponding arylthiophenols.

The sulfides **4** thus obtained were oxidized into sulfone derivatives using hydrogen peroxide in the presence of a catalytic amount of sodium tungstate as a reagent system to get a set of sulfones **5**. All the sulfide (**4a-d**) and sulfone (**5a-d**) analogues (Figure 2) were tested against the *Mycobacterium tuberculosis* $H_{37}R_V$ strain.

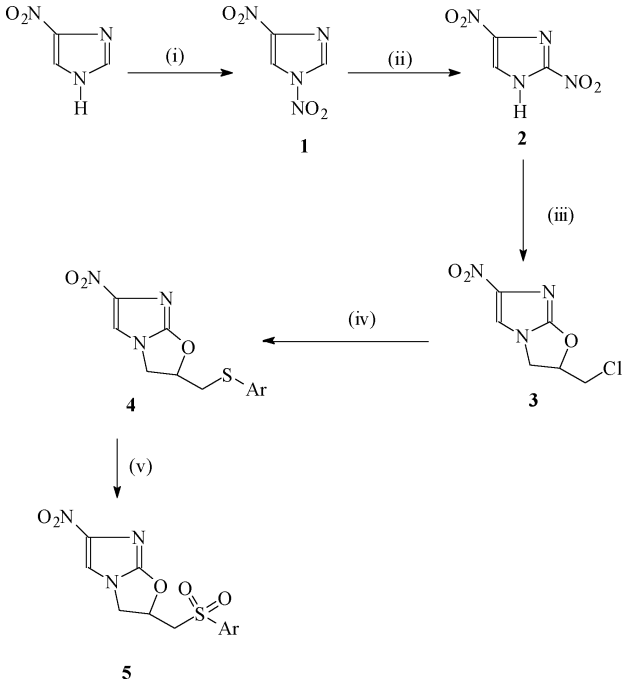


4
4a,
4b,
4c,
4d,

5
5a Ar = 2-thienyl;
5b, Ar = phenyl;
5c, Ar = 4-chlorophenyl;
5d, Ar = 4-methylphenyl

Figure 2. Chemical structures of racemic sulfides and sulfones synthesized and tested against the *M. tuberculosis* $H_{37}Rv$ strain.

Scheme 1



Reagents, conditions and isolated yields: (i) AcOH, Fuming nitric acid (Sp. Gr. 1.52) and Ac_2O, 67.60%. (ii) MW/solvent, 79 % (iii) Epichlorohydrin/ EtOH, reflux, 24 h, 22% (iv) ArSH, K_2CO_3, DMF, rt, 22-35% (v) 30% H_2O_2, $Na_2WO_4.2H_2O$, Ethyl acetate: water (5:1), rt, 55-65%.

Results and Discussion.

All microwave reactions were carried out by simply irradiating a solution of 1,4-DNI in a suitable solvent by using household microwave oven (IFB make) modified with refluxing system; and a power of 750 watts with maximum frequency of 2450 MHz. The reaction was standardized with respect to solvent, concentration, reaction time, and power level of irradiation. The best results are tabulated in Table 1.

Table 1

MW Assisted Rearrangement of 1,4-DNI to 2,4-DNI

Solvent	Concentration (%) [a]	Power Level (%)	Time of Exposure (min)	Yields (%) [b]
PhCl	10	90	10	51
PhCN	10	50	2	79
PhCN:PhCl (3:7)	10	90	5	71

[a] 10% was found to be an optimum concentration; at higher concentration colored impurities developed; [b] yields are the isolated yields after silica gel column chromatography.

To have a ready comparison side by side with the conventional heating, a set of parallel experiments were performed. In all cases the reaction required longer times. The results are given in Table 2.

Table 2

Comparative Results of Conventional Heating, MW assisted, and Molten state Rearrangement of 1,4-DNI to 2,4-DNI

Series No.	Solvent	Temp. (°C)	Time (h/min)	Yields (%)	Reference
1	PhCl	125-130	50 h	80	1d
2	PhCN	125-130	12 h	51	--
3	PhCN:PhCl (3:7)	125-130	12 h	48	--
4	PhCN	MW	2 min	79	-
5	---	95-98 (Molten State)	25 min	No reaction	1a

To demonstrate the microwave activity of 1,4-DNI in PhCN a series of parallel experiments were run and the temperatures were recorded at the end of 1 min of exposure (by external thermometer) at 50% power level. Figure 3 clearly shows that 1,4-DNI is microwave active, since in the initial one minute temperature rises with increase in the concentration of 1,4-DNI.

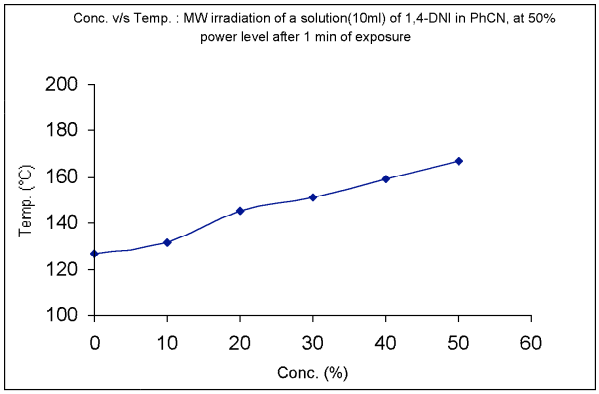


Figure 3

The studies showed that conversion of 1,4-DNI increases as the concentration increases up to 30% with no significant increase in conversion thereafter (Figure 4). However, formation of colored impurities and decomposition were observed at 20% concentration and above.

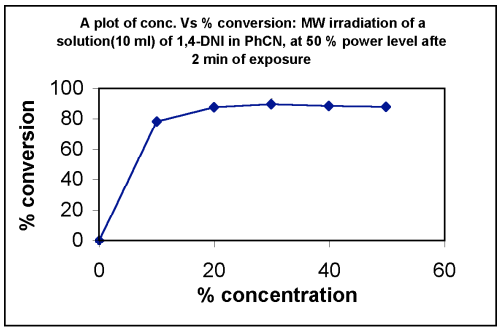


Figure 4

Therefore, 10% was chosen as an optimum concentration for subsequent experiments. The reactions were repeated several times and results were highly reproducible. No explosions were experienced. Nevertheless care must be taken for potential explosion hazards. In all the reactions performed, formation of 4-nitroimidazole was observed. The rearrangement was also attempted by microwave irradiation of a neat pure crystalline sample of 1,4-DNI and also 1,4-DNI on silica gel. In the former case an explosion took place (**CAUTION!**) and in the latter decomposition occurred where charred material was obtained with small amounts of 2,4-DNI.

The various synthesized nitroimidazooxazoles were tested preliminarily against $H_{37}Rv$ strain. Minimum Inhibitory Concentrations (MICs) were considerably low, however, some of the compounds showed activity at 200 μg/ml (Table 3). There was no clear structural relationship of the synthesized analogues with respect to observed activity. These newly tested analogues may be of interest to medicinal chemists, for further structural variation and to get some insight into structural requirements.

Conclusion.

An improved and a convenient method based on microwave irradiation has been developed for the synthesis of 2,4-DNI. Using 2,4-DNI various sulfide and sulfone analogues of nitroimidazooxazoles were prepared. All the newly synthesized analogues were screened for antimycobacterial activity against $H_{37}Rv$ strain. Some of these analogues showed moderate antitubercular activity.

EXPERIMENTAL

Melting points are uncorrected. Infrared (IR) spectra were recorded on BUCK Scientific IR Spectrometer and ^1H NMR recorded on 60 MHz JEOL NMR. Mass spectra were recorded on a Finnigan Mat 1020B Mass Spectrometer and using EI at 70 eV for ionization. The Microwave reactions were carried out using an IFB make household microwave oven modified with refluxing system, and a power of 750 watts with a maximum frequency of 2450 MHz. Unless otherwise specified, reagents used for the synthesis were obtained commercially.

Table 1

Activity Test Tesults Against *Mycobacterium tuberculosis* $H_{37}Rv$ Strain

Compound No (Figure 2)	*In vitro* activity (MIC, μg/ml) [a,b,c]
3	200
4a	-
4b	-
4c	-
4d	200
5a	200
5b	-
5c	200
5d	-

[a] All results were recorded in form of minimum inhibitory concentration (MIC) defined as the minimum drug concentrations to inhibit the growth of *M. tuberculosis* strain $H_{37}Rv$; [b] all compounds are soluble in DMSO and range of concentration used 200 μg/ml- 2 μg/ml (blank cell indicate in this concentration range compound is inactive); [c] MIC of CGI-17341 (**I**) is 0.06 μg/ml and PA-824 (**II**) is 0.015 μg/ml.

1,4-Dinitroimidazole (1,4-DNI) **1**.

A stirred solution of 4-nitroimidazole (10.00 g, 88.5 mmol) in glacial acetic acid (20 mL) was cooled to 0 °C by external cooling in an ice-bath. Freshly prepared fuming nitric acid (6.5 mL) (Sp.gr 1.52) was added slowly followed by addition of acetic anhydride (18 mL). Contents of the flask were stirred at this temperature till complete dissolution of solid takes place and solution becomes golden yellow in colour (about 2 h). The mixture was stirred at room temperature overnight. Reaction was quenched by pouring the contents into ice-cold water (125 mL) with vigorous stirring and the solid precipitated was collected by filtration and washed with ice-cold water (about 100 mL). This solid was further purified by recrystallization from benzene to give 1,4-DNI as white fine needles (9.45 g, 67.60%). m.p. 92 °C (Lit. [1a], 92 °C); ^1H-NMR ($CDCl_3$) δ 8.7 (s, 1H, H-5), 8.5 (s, 1H, H-2).

Microwave Preparation of 2,4-Dinitroimidazole (2,4-DNI) **2**.

Caution!: *We never experienced any explosion in any of our experiments and while handling 1,4-DNI and 2,4-DNI. However, we would like to caution that these compounds are potential explosives [1a], and care must be taken while carrying out these reactions.*

1,4-DNI (1.0 g, 6.33 mmol) was taken in benzonitrile (10 mL) and irradiated in a microwave oven at 50% power level for 2 min. The reaction mixture was cooled to room temperature and the solid precipitated was collected by filtration to give crude 2,4-DNI. The mother liquor was treated with hexane (25 mL) to recover a second crop of 2,4-DNI. The crude 2,4-DNI was purified by silica gel (60-120 mesh) chromatography using ethyl acetate:hexane (8:2) to give crystalline 2,4-DNI (0.79 g, 79%). 2,4-DNI can also be purified by recrystallization from a mixture of acetonitrile and chloroform. m.p. 264-267 °C (Lit. [1c], 264-

Table 2

Physical Constant and Spectral Data

No.	Yield (%)	Melting Point (°C)/State (recryst solvent)	NMR and MS
3	22	170-171(White solid) (ethanol)	d 8.03 (s, 1H, H-5); 5.60 (m, 1H, H-2); 4.58-4.05 (m, 4H, H-3 & CH_2Cl). MS (EI): m/z 205/203 (M^+, ^{37}Cl/ M^+, ^{35}Cl), 189/187, 170/168, 159/157, 147/145, 131/129, 118, 102, 93, 83, 75, 67, 56, 41(base peak). *Anal*. Calcd. for $C_6H_6N_3O_3Cl$: C, 35.38; H, 2.93; N, 20.60 ;Cl, 17.44. Found: C, 35.32; H, 2.91; N, 20.00; Cl, 17.49.
4a	30	184-185(White solid) (benzene)	δ 8.03 (s, 1H, H-5), 7.18 (m, 1H, thiophene), 7.11-6.98 (m, 2H, thiophene), 5.44-5.24 (m, 1H, H-2), 4.38-4.01(m, 2H, H-3), 2.39 (m, 1H, CH_2S). MS (EI): m/z 283 (M^+), 255, 237, 227, 206, 149, 129, 115(base peak), 91, 71, 57, 41. *Anal*. Calcd. for $C_{10}H_{10}N_3O_3S_2$: C, 42.25; H, 3.52; N, 14.79; S, 22.54. Found: C, 42.11; H, 3.51; N, 14.72; S, 22.55.
4b	35	174-175 (light yellow solid) (benzene)	δ 8.03(s, 1H, H-5), 7.29 (m, 5H, aromatic), 5.63-5.23(m, 1H, H-2), 4.56-4.04 (m, 2H, H-3), 2.43 (m, 2H, CH_2S). MS(EI): m/z 277(M^+), 203, 149, 135, 123, 109, 93, 77, 67, 41(base peak). *Anal*. Calcd. for $C_{12}H_{11}N_3O_3S$: C, 51.99; H, 3.97; N, 15.16; S, 11.55. Found: C, 51.85; H, 3.93; N, 15.11; S, 11.59.
4c	30	168-169 (Yellowish solid) (benzene)	δ 8.03 (s, 1H, H-5), 7.79-7.31(m, 4H, aromatic), 5.54-5.29(m, 1H, H-2), 4.38-4.00 (m, 2H, H-3), 2.38(m, 2H, CH_2S). MS (EI): m/z 313/311(M^+, ^{37}Cl/ M^+, ^{35}Cl), 239/237, 200, 183, 169, 159/157(base peak), 145/143,108, 93, 67, 41. *Anal*. Calcd. for $C_{12}H_{10}N_3O_3SCl$: C, 46.22; H, 3.21; N, 13.48; S, 10.27; Cl, 11.39. Found: C, 46.20; H, 3.11; N, 13.42; S, , 10.30; Cl 11.30
4d	32.50	165-166(White solid) (benzene)	δ 8.03 (s, 1H, H-5), 7.18 (m, 1H, thiophene), 7.11-6.98 (m, 2H, thiophene), 5.44-5.24 (m, 1H, H-2), 4.38-4.01(m, 2H, H-3), 2.39(m, 1H, CH_2S). MS (EI): m/z 283 (M^+), 255, 237, 227, 206, 149, 129, 115(base peak), 91, 71, 57, 41. *Anal*. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.61; H, 4.47; N, 14.43; S, 11.00. Found: C, 53.58; H, 4.46; N, 14.41; S, 11.02.
5a	61	160-161 (White solid) (benzene)	MS(EI): m/z 315 (M^+), 287, 149. *Anal*. Calcd. for $C_{10}H_9N_3O_5S_2$: C, 37.97; H, 3.16; N, 13.29; S, 20.25. Found: C, 37.91; H, 3.06; N, 13.30; S, 20.50.
5b	70	212-214(Yellowish solid) (benzene)	MS(EI): m/z 309 (M^+), 235, 41. *Anal*. Calcd. for $C_{12}H_{11}N_3O_5S$: C, 46.60; H, 3.56; N, 13.59; S, 10.36. Found: C, 46.52; H, 3.55; N, 13.57; S, 10.38.
5c	55.50	206-208(White solid) (benzene)	MS(EI): m/z 345/343 (M^+, ^{37}Cl,/^{35}Cl),271/269,149,41. *Anal*. Calcd. for $C_{12}H_{10}N_3O_5SCl$: C, 41.92; H, 2.91; N, 12.22; S, 9.32; Cl, 10.33. Found: C, 41.88; H, 2.90; N, 12.21; S, 9.33; Cl 10.38
5d	65	174-175(White solid) (benzene)	Mass Spectra (EI): m/z 323(M^+), 278,246,149. *Anal*. Calcd. for $C_{13}H_{13}N_3O_5S$: C, 48.29; H, 4.02; N, 13.00; S, 9.91. Found: C, 48.20; H, 3.98; N, 13.02; S, 9.99.

267 °C); ^{1}H-NMR ($CDCl_3$+ DMSO-d_6): δ 9.6 (s, 1H (exchanges with D_2O), N*H*), 8.60 (s, 1H, H-5).

Anal. Calcd. for $C_3H_2N_4O_4$: C, 22.72; H, 1.27; N, 35.44. Found: C, 22.72; H, 1.25; N, 35.41.

2-Chloromethyl-2,3-dihydro-6-nitroimidazo[2,1-*b*]oxazole (**3**).

A mixture of 2,4-DNI **2**, (2.5 g, 5.80 mmol), absolute ethanol (100 mL) and epichlorohydrin (25 mL) was heated under reflux for 20 h. Solvent was removed under rotary evaporator and the residue obtained was treated with hexane (30 mL), and allowed to settle. The upper hexane layer was decanted and to the remaining thick slurry was added a chloroform:methanol mixture (2:1) (15 mL) with stirring. The solid that precipitated was collected by filtration, dried and was recrystallized from boiling ethanol to give the product **3** (0.70 g, 22%), m.p. 170-171 °C (Lit. [3,5b], 170-171 °C); IR (KBr): 1607, 1516, 1472, 1459, 1335, 1319, 746; ^{1}H-NMR (DMSO-d_6): δ 8.03 (s, 1H, H-5), 5.60 (m, 1H, H-2), 4.58-4.05 (m, 4H, H-3 & CH_2Cl); MS (EI): m/z 205/203 (M^+, ^{37}Cl/ M^+, ^{35}Cl), 189/187, 170/168, 159/157, 147/145, 131/129, 118, 102, 93, 83, 75, 67, 56, 41 (base peak).

2-(4-Methylthiophenoxy)methyl-2,3-dihydro-6-nitroimidazo[2,1-*b*]oxazole (**4d**).

Compound **3** (100 mg, 0.49 mmol) and 4-methylthiophenol (61 mg, 0.49 mmol) were taken in dry DMF (2 mL) with potassium carbonate (68 mg, 0.49 mmol). The reaction mixture was then stirred at room temperature for 10 min. It was quenched with copious volume of water (*ca*. 30 mL). The solid separated out was collected by filtration, washed with dilute sodium hydroxide solution and purified by crystallization from boiling benzene to give **4d** as white solid (50 mg, 32.65%). m.p.,165-166 °C, IR (KBr): 3099, 2910, 1604, 1511, 1460, 1318, 1282, 1119, 1081, 987, 800, 701; ^{1}H-NMR (DMSO-d_6): δ 8.03 (s, 1H, H-5), 7.46-7.18 (m, 4H, aromatic), 5.49-5.31 (m, 1H, H-2), 4.56-3.97 (m, 2H, H-3), 2.41 (m, 2H, CH_2S), 2.12 (s, 3H, CH_3); MS (EI): m/z 291(M^+), 279, 245, 217, 167, 149 (base peak), 137, 123, 91, 79, 67, 57.

Anal. Calcd. for $C_{13}H_{13}N_3O_3S$: C, 53.61; H, 4.47; N, 14.43; S, 11.00. Found: C, 53.58; H, 4.46; N, 14.41; S, 11.02.

Compounds **4a, 4b, 4c** were also synthesized by the above procedure.

2-(4-Methylphenylsulfonyl)methyl-2,3-dihydro-6-nitroimidazo[2,1-*b*]oxazole (**5d**).

To a stirred slurry of compound **4d** (50 mg, 0.171 mmol) and sodium tungstate dihydrate (5 mg, 0.015 mmol) in ethyl acetate:water (12 mL, 5:1) was added H_2O_2 (30 %v/v, 5 mL) and stirring was continued for 2 h. Then, the reaction was quenched by addition of saturated sodium bisulfite solution (5 mL) followed by extraction with ethyl acetate (2 × 25 mL). The organic layer was dried over sodium sulfate and evaporated under vacuum. The solid obtained was crystallized from hot benzene to give **5d** as white solid (36mg. 64.88%), m.p. 174-175 °C; MS (EI): m/z 323(M^+), 278 (base peak), 262, 246, 167, 149, 107, 65, 44.

Anal. Calcd. for $C_{13}H_{13}N_3O_5S$: C, 48.29; H, 4.02; N, 13.00; S, 9.91. Found: C, 48.20; H, 3.98; N, 13.02; S, 9.99.

Compound **5a, 5b, 5c** were also synthesized by the above procedure.

Pharmacology Methods.

Bacterial Strains.

The bacterial strain used in this study was *M. tuberculosis* H_{37}Rv, which served as the wild type strain of *M. tuberculosis*.

Determination of MICs.

The bacterial suspension were prepared by diluting organisms grown in Middle brook 7H9 broth medium (with ADC supplement) at 37 °C for 10 days with 0.05% Tween 80 in distilled water to give a bacterial concentration of *ca.* 10^6 cfu/ml. The bacterial suspension 0.1 ml was taken in test tubes (*ca*. 10 ml volume) containing 200-2 μg of drug per mL. The drugs were initially dissolved in DMSO and the required amount was added to the broth medium (with ADC supplement) containing 0.05% Tween 80 in distilled water. The MICs of the drugs were determined 14 days after the start of cultivation at 37 °C in incubator. The MICs of the drugs were determined as the minimum drug concentrations for complete inhibition of organism growth.

Acknowledgments.

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[2] RDX (Royal Demolition explosive) is cyclotrimethylenetrinitramine, HMX (High melting explosive), is cycloteramethylenetetramine, and TATB is triamino-tribenzene.

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