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Synthesis and Characterization of Hydrazide-Hydrazone Derivatives of 3-Pyridine Carboxylic Acid as Antimycobacterial Tuberculosis Agents

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In this study synthesis of nicotinoyl hydrazone derivatives is investigated by introducing the nicotinicacidhydrazidepharmacophore into several molecules and screening for antimycobacterial activity. Benzaldehyde derivatives react with nicotinicacidhydrazideto form nicotinoylhydrazones.The synthesized compounds were screened against *M. tuberculosis* $H_{37}Rv$, clinical isolates of *M. tuberculosis* and MDR clinical isolates of *M. tuberculosis*using the proportion test. The minimum inhibitory concentration (MIC) of *N'*-(4-methylphenyl) nicotinicacidhydrazone and *N'*-(4-(*N*,*N*-dimethyl)phenyl)nicotinicacidhydrazone exhibited activity between 40 and 200µg/mL and could be a good start point to find new lead compounds against *M. tuberculosis*.

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Introduction

According to alarming data from the World Health Organization, tuberculosis (TB) has spread to every corner of the globe [1].About 32% of the world's population (1.9 billion people) is infected with TB. Every year, approximately 8 million of these infected people develop active TB, and almost 2 million of them die from the disease [2].The global resurgence of TB has been favored by: (a) the diffusion of the human immunodeficiency virus (HIV) and the deadly synergy of TB and non-tubercular mycobacterial infections with HIV [3-6]. (b) The widespread emergence of resistant strains of *Mycobacterium tuberculosis*, which are insensitive to one or more of the first-line anti-TB drugs [7-12].Recently, it was suggested that the mechanism of resistance to INH is related to katG mutations and deletions, and secondly to chromosomal mutations in inhA and kasA [13].Antibacterial resistance to a drug can be counteracted by designed new derivatives [14].Here, we report the synthesis and preliminary antimycobacterial activity data of nicotinoyl hydrazones.

Materials and Methods

Chemistry

Nicotinoylhydrazones **1–14** described in this study is shown in Table 1, and a reaction sequence for the preparation is outlined in Figure 1. Benzaldehyde derivatives react with nicotinicacidhydrazidein ethanolic medium for 1.5 h to form nicotinoyl-hydrazonesin yields 87-96%.

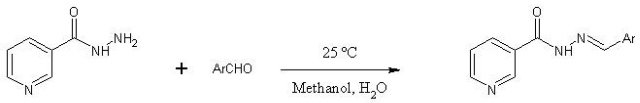
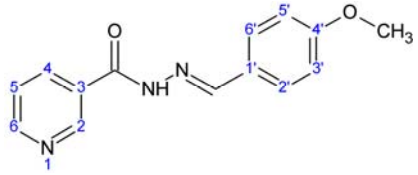


Fig. 1. Reaction sequence for the preparation**.**

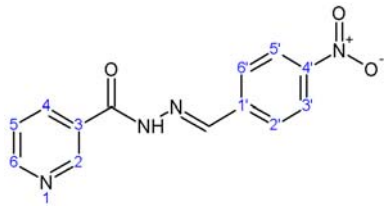
The purity of the compounds was checked by TLC and melting point, and the synthesized compounds were identified by spectral data.

N'-(4-Methoxyphenyl)nicotinicacidhydrazone (**1**).Mp = 104 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 2.36 (s, 3H, CH_3), 7.29 (d, *J*= 8 Hz, 2H, C_3·H), 7.56-7.58 (dd, *J*=5, *J*=2.5Hz, 1H, C_5H), 7.65 (d, *J*=8Hz, 2H, C_2·H), 8.25-8.26 (m, 1H, C_4H), 8.41 (s, 1H, CH=N), 8.76 (d, *J*=3.5Hz, 1H, C_6H), 9.07 (s, 1H, C_2H), 11.96 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.3 (CH_3), 123.5 (C_5), 127.1 (C_3·, C_5·), 129.2 (C_3), 129.4 (C_2·, C_6·), 131.4 (C_1·), 135.4 (C_4), 148.4 (C_6), 148.5 (C=N), 149.9 (C_4·), 152.2 (C_2), 161.5 (C=O) ppm.



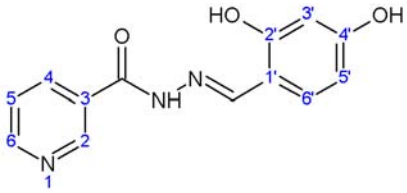
1

N'-(4-Nitrophenyl)nicotinicacidhydrazone (**2**)Mp = 259 °C, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.57-7.60 (dd, *J*=5, *J*=2.5Hz, 1H, C_5H), 7.99-8.01 (d, *J* =8.5Hz, 2H, C_2·H), 8.26-8.30 (m, 1H, C_4H), 8.26-8.30 (m, 2H, C_3·H) 8.53 (s, 1H, CH=N), 8.78 (d, *J*=4Hz, 1H, C_6H), 9.08 (s, 1H, C_2H), 12.30 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 123.6 (C_5), 124.0 (C_3·, C_5·), 128.1 (C_2·, C_6·), 128.8 (C_3), 135.5 (C_4), 140.4 (C_1·), 145.8 (C_4·), 147.7 (C=N), 148.6 (C_6), 152.5 (C_2), 162.0 (C=O)ppm.



2

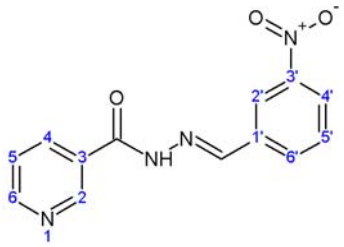
N'(2,4Dihydroxyphenyl)nicotinicacidhydrazone (**3**).Mp = 290 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 6.34 (s , 1H, C_1·H), 6.36-6.38 (d, *J*=10Hz, 1H, C_6·H), 7.34-7.36 (d, *J* = *8.5*Hz, 1H, C_5·H), 7.56-7.58 (dd, *J*=5, *J*=2.5Hz, 1H, C_5H),8.25-8.27 (d, *J* = *8*Hz, 1H, C_4H), 8.51 (s, 1H, CH=N), 8.76-8.77 (d, *J*=3.5Hz, 1H, C_6H), 9.07 (s, 1H, C_2H),10.01 (s, 1H, C_2·OH), 11.34 (s, 1H, C_4·OH), 12.08 (s, 1H, NH)ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 102.6 (C_3·), 107.8 (C_5·), 110.4 (C_1·), 123.6 (C_5), 128.8 (C_3), 131.2 (C_6·), 135.3 (C_4), 148.5 (C_6), 149.5 (C=N), 152.3 (C_2), 159.5 (C_2·), 160.9 (C_4·), 161.1 (C=O)ppm.



3

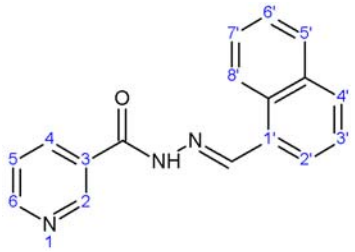
N'-(3-Nitrophenyl)nicotinicacidhydrazone (**4**).Mp = 187 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 7.57-7.59 (dd, *J*=5, *J*=2.5Hz, 1H, C_5H), 7.75-7.78 (t, *J*=*8*Hz, 1H, C_5·H), 8.18-

8.19 (d, *J=7.5*Hz, 1H, $C_{6'}H$), 8.27-8.28 (m, 1H, C_4H), 8.27-8.28 (m, 1H, $C_{4'}H$), 8.56 (s, 1H, CH=N), 8.57 (s, 1H, $C_{2'}H$), 8.77-8.78 (d, *J*=3.5Hz, 1H, C_6H), 9.08 (s, 1H, C_2H), 12.27 (s, 1H, NH)ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 122.9 ($C_{2'}$), 123.5 (C_5), 124.3 ($C_{4'}$), 128.8 (C_3), 130.4 ($C_{5'}$), 133.3 ($C_{6'}$), 135.5 (C_4), 136.0 ($C_{1'}$), 145.8 ($C_{3'}$), 148.1 (C_6), 148.6 (C=N), 152.3 (C_2), 161.8 (C=O)ppm.



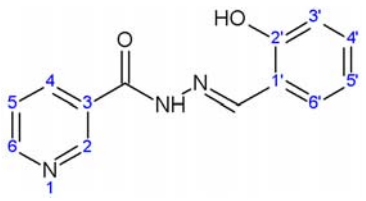
4

N'-(1-naphthyl)nicotinicacidhydrazone (**5**).Mp = 187 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 7.56-7.58 (dd, *J*=5, *J*=2.5Hz, 1H, C_5H),8.25-8.26 (m, 1H, C_4H), 8.41 (s, 1H, CH=N), 8.76 (d, *J*=3.5Hz, 1H, C_6H), 9.07 (s, 1H, C_2H), 11.96 (s, 1H, NH)ppm.



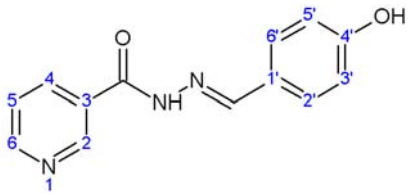
5

N'-(2-Hydroxyphenyl)nicotinicacidhydrazone (**6**).Mp = 185 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 6.92-6.96 (m, 2H, $C_{4'}H$, $C_{5'}H$), 7.30-7.33 (t, *J=7*Hz, 1H, $C_{6'}H$), 7.57-7.60 (m, 2H, C_5H, $C_{3'}H$),8.27-8.30 (m, 1H, C_4H), 8.66 (s, 1H, CH=N), 8.81-8.88 (d, *J*=3.5Hz, 1H, C_6H), 9.07 (d, *J=2*Hz, 1H, C_2H), 11.15 (s, 1H, $C_{2'}OH$), 12.27 (s, 1H, NH)ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 116.4 ($C_{3'}$), 118.6 ($C_{5'}$), 119.4 ($C_{1'}$), 123.6 (C_5), 128.6 (C_3), 129.3 ($C_{4'}$), 131.6 ($C_{6'}$), 135.5 (C_4), 148.5 (C_6), 148.6 (C=N), 152.4 (C_2), 157.4 ($C_{2'}$), 161.4 (C=O)ppm.



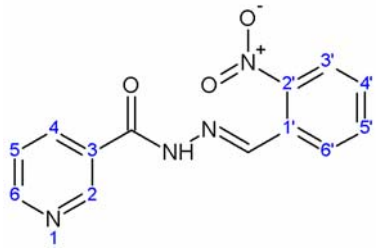
6

N'-(4-Hydroxyphenyl)nicotinicacidhydrazone (**7**).Mp = 248 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 6.85-6.86 (d, *J=8.5*Hz, 2H, $C_{3'}H$, $C_{5'}H$), 7.54-7.57 (dd, *J*=5, *J=2.5*Hz, 1H, C_5H), 7.58-7.59 (d, *J=8.5*Hz, 2H, $C_{2'}H$, $C_{6'}H$), 8.24-8.25 (m, 1H, C_4H), 8.35 (s, 1H, CH=N), 8.75 (d, *J*=3Hz, 1H, C_6H), 9.06 (s, 1H, C_2H), 9.99 (s, 1H, $C_{4'}H$), 11.83 (s, 1H, NH)ppm; ^{3}C NMR (DMSO-d_6, 100 MHz): δ 115.7 ($C_{3'}$, $C_{5'}$), 123.6 (C_5), 125.1 ($C_{1'}$), 129.0 ($C_{2'}$, $C_{6'}$), 129.3 (C_3), 135.3 (C_4), 148.5 (C_6), 148.7 (C=N), 152.1 (C_2), 159.6 ($C_{4'}$), 161.4 (C=O)ppm.



7

N'-(2-Nitrophenyl)nicotinicacidhydrazone (**8**).Mp = 193 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 7.57-7.59 (dd, *J = 5*, *J= 2.5*Hz, 1H, C_5H), 7.70 (t, *J=7.5*Hz, 1H, $C_{4'}H$), 7.83 (t, *J=7.5*Hz, 1H, $C_{5'}H$), 8.09-8.10 (d, *J=8*Hz, 1H, $C_{3'}H$), 8.13-8.15 (d, *J=8*Hz, 1H, $C_{6'}H$), 8.28-8.30 (m, 1H, C_4H), 8.86 (s, 1H, CH=N), 8.78 (d, *J =4*Hz, 1H, C_6H), 9.09 (s, 1H, C_2H), 12.37 (s, 1H, NH)ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 123.6 (C_5), 124.7 ($C_{3'}$), 128.0 ($C_{6'}$), 128.5 ($C_{1'}$), 128.7 (C_3), 130.8 ($C_{4'}$), 133.8 ($C_{5'}$), 135.5 (C_4), 143.7 ($C_{2'}$), 148.7 (C_6), 149.8 (C=N), 152.5 (C_2), 161.9 (C=O)ppm.

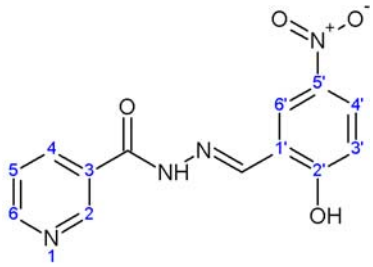


8

N'-(2,5-Dihydroxyphenyl)nicotinicacidhydrazone (**9**).Mp = 271 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 6.74-6.78 (m, 2H, $C_{3'}H$, $C_{4'}H$), 7.03 (d, *J=2.5*Hz, 1H, $C_{6'}H$), 7.56-7.58 (dd, *J*=5, *J*=2.5Hz, 1H, C_5H),8.27-8.28 (m, 1H, C_4H), 8.59 (s, 1H, CH=N), 8.76-8.77 (d, *J=4*Hz, 1H, C_6H), 9.00 (s, 1H, $C_{2'}OH$), 9.09 (s, 1H, C_2H), 10.27 (s, 1H, $C_{5'}OH$), 12.14 (s, 1H, NH)ppm.

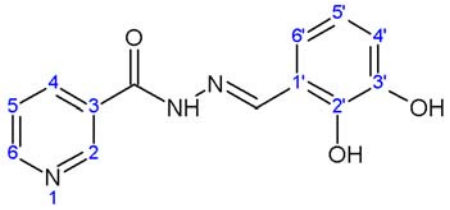
9

N'-(2-Hydroxy-5nitrophenyl)nicotinicacidhydraone (**10**). Mp = 281 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 7.11-7.12 (d, *J*=9Hz, 1H, $C_{4'}$H), 7.58-7.60 (dd, *J*=5, *J*=2.5Hz, 1H, C_5H), 8.17-8.19 (dd, *J*=2.5, *J*=6.5, 1H, $C_{3'}$H), 8.28-8.30 (m, 1H, C_4H), 8.60-8.61 (d, *J*=3Hz, 1H, $C_{6'}$H), 8.74 (s, 1H, CH=N), 8.78-8.79 (d, *J*= 3.5Hz, 1H, C_6H), 9.10 (s, 1H, C_2H), 12.24 (s, 1H, $C_{2'}$OH), 12.39 (s, 1H, NH)ppm; ^{13}C NMR (DMSO-d_6,100 MHz): δ 117.1 ($C_{3'}$), 120.0 ($C_{1'}$), 123.5 ($C_{6'}$), 123.6 (C_5), 126.7 ($C_{4'}$), 128.5 (C_3), 135.5 (C_4), 139.9 ($C_{5'}$), 144.5 (C=N), 148.6 (C_6), 152.5 (C_2), 161.7 (C=O), 162.5 ($C_{2'}$)ppm.



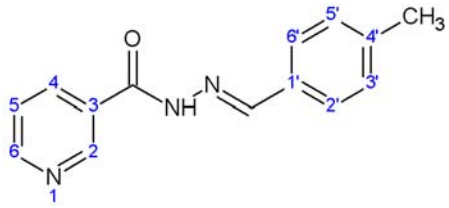
10

N'-(2,3-Dihydroxyphenyl)nicotinicacidhydrazone (**11**).Mp = 231 °C,^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.74-6.77 (t, *J* = 7.5 Hz, 1H, $C_{5'}$H), 6.87-6.89 (dd, *J* = 1.5, *J* = 6.5 Hz, 1H, $C_{4'}$H), 7.00-7.02 (dd, *J* = 1.5, *J* = 6 Hz, 1H, $C_{6'}$H), 7.58-7.60 (dd, *J* = 5, *J* = 2.5 Hz, 1H, C_5H),8.27-8.30 (m, 1H, C_4H), 8.61 (s, 1H, CH=N), 8.78-879 (dd, *J* = 3,*J* = 1.5 Hz, 1H, C_6H), 9.1• (s, 1H, C_2H), 9.29 (s, 1H, $C_{3'}$OH), 10.96 (s, 1H, $C_{2'}$OH), 12.26 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 117.5 ($C_{4'}$), 118.7 ($C_{1'}$), 119.2 ($C_{6'}$), 119.9 ($C_{5'}$), 123.6 (C_5), 128.6 (C_3), 135.4 (C_4), 145.6 ($C_{2'}$), 146.1 ($C_{3'}$), 148.6 (C_6), 149.3 (C=N), 152.4 (C_2), 161.4 (C=O)ppm.



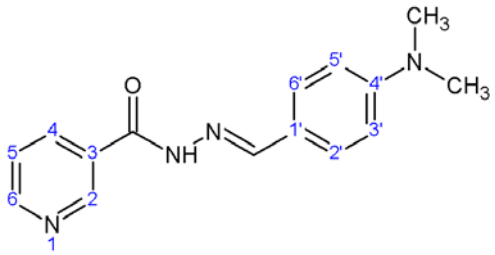
11

N'-(4-Methylphenyl)nicotinicacidhydrazone (**12**).Mp = 113 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 2.36 (s, 3H, CH_3), 7.28-7.30 (d, *J*=7.5 Hz, 2H, $C_{3'}$H, $C_{5'}$H), 7.56-7.59 (dd, *J*=5, *J*=2.5 Hz, 1H, C_5H), 7.64-7.66 (d, *J*=8 Hz, 2H, $C_{2'}$H, $C_{6'}$H), 8.25-8.26 (m, 1H, C_4H), 8.41 (s, 1H, CH=N), 8.76-8.77 (d, *J*=5 Hz, 1H, C_6H), 9.07 (s, 1H, C_2H), 11.96 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.0 (CH_3), 123.5 (C_5), 127.1 ($C_{2'}$, $C_{6'}$), 129.2 (C_3), 129.4 ($C_{3'}$, $C_{5'}$), 131.4 ($C_{1'}$), 135.4 (C_4), 140.1 ($C_{4'}$), 148.4 (C_6), 148.5 (C=N), 152.2 (C_2), 161.5 (C=O) ppm.



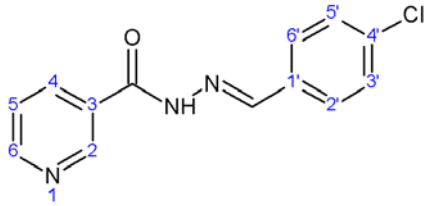
12

N'-(4-(N,Ndimethyl)phenyl)nicotinicacidhydrazone (**13**).Mp = 136 °C.^{1}H NMR (DMSO-d_6):δ 2.98 (s, 6H, NMe2), 6.75-6.77 (d, *J*=9 Hz, 2H, $C_{3'}$H, $C_{5'}$H), 7.55-7.57 (m, , 3H, C_5H, $C_{2'}$H, $C_{6'}$H),8.23-8.24 (m, 1H, C_4H), 8.30 (s, 1H, CH=N), 8.74-8.75 (d, *J*=3.5 Hz, 1H, C_6H), 9.05 (s, 1H, C_2H), 11.72 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 40.0 (Me_2), 111.7 ($C_{3'}$, $C_{5'}$), 121.3 ($C_{1'}$), 123.5 (C_5), 128.5 ($C_{2'}$, $C_{6'}$), 129.5 (C_3), 135.2 (C_4), 148.4 (C_6), 149.2 (C=N), 151.6 ($C_{4'}$), 152.0 (C_2), 161.1 (C=O) ppm.



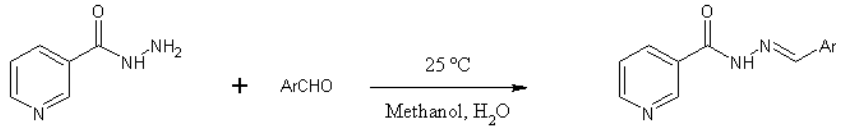
13

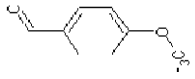
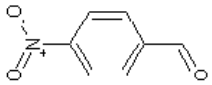
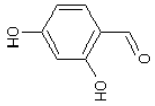
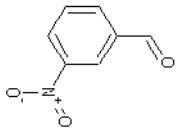
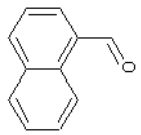
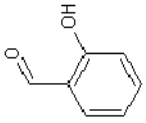
N'-(4-Chlorophenyl)nicotinicacidhydrazone (**14**).Mp = 184 °C,^{1}H NMR (DMSO-d_6, 500 MHz):δ 7.53-7.55 (d, *J*=9, 2H, $C_{2'}$H, $C_{6'}$H), 7.56-7.59 (dd, *J*=5, *J*=2.5, 1H, C_5H), 7.77-7.79 (d, *J*=8, 2H, $C_{3'}$H, $C_{5'}$H), 8.25-8.27 (m, 1H, C_4H), 8.44 (s, 1H, CH=N), 8.77-8.78 (d, *J*=3.5, 1H, C_6H), 9.07 (s, 1H, C_2H), 12.10 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 123.6 (C_5), 128.8 ($C_{3'}$, $C_{5'}$), 128.9 ($C_{2'}$, $C_{6'}$), 129.0 (C_3), 133.0 ($C_{1'}$), 134.7 ($C_{4'}$), 135.4 (C_4), 147.0 (C=N), 148.5 (C_6), 152.3 (C_2), 161.7 (C=O) ppm.



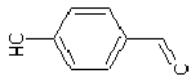
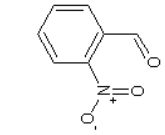
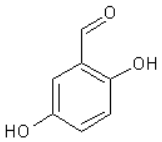
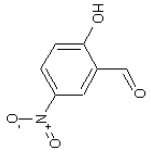
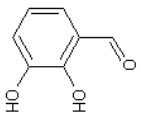
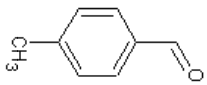
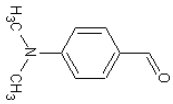
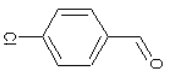
14

Table1.



Compound	Ar	Molecular formula	Yield(%)	Time(h)	Mp(°C)	log*P*	MIC(μg/ml)		
							$H_{37}Rv$	clinical	MDR
1		$C_{14}H_{13}O_2N_3$	91	1.5	104	3.6	>200	>200	>200
2		$C_{13}H_{10}O_3N_4$	88	1.5	259	1.4	>200	>200	>200
3		$C_{13}H_{11}O_3N_3$	90	1	290	1.25	100	200	>200
4		$C_{13}H_{10}O_3N_4$	93	1.5	187	1.4	200	200	>200
5		$C_{17}H_{13}ON_3$	87	1.5	186	3.2	>200	>200	100
6		$C_{13}H_{11}O_2N_3$	96	1.5	185	1.64	>200	>200	>200

Continue Table 1.

Compound	Ar	Molecular formula	Yield(%)	Time(h)	Mp(°C)	log*P*	MIC(µg/ml)		
							$H_{37}Rv$	clinical	MDR
7		$C_{13}H_{11}O_2N_3$	95	1.5	248	1.64	100	>200	>200
8		$C_{13}H_{10}O_3N_4$	92	1.5	193	1.4	200	>200	200
9		$C_{13}H_{11}O_3N_3$	90	1	271	1.25	100	100	200
10		$C_{13}H_{10}O_4N_4$	90	1.5	281	1.1	200	200	>200
11		$C_{13}H_{11}O_3N_3$	89	1	231	1.25	200	200	200
12		$C_{14}H_{13}ON_3$	90	1.5	113	2.51	40	40	200
13		$C_{15}H_{16}ON_4$	90	1.5	136	2.31	40	40 200	>200 200
14		$C_{13}H_{10}ON_3Cl$	93	1	184	2.59	200	200	200
isoniazid	-	-	-	-	-	-	0.2	0.2	-

Antimycobacterial activity

The synthesized compounds **1–14**were tested for their antimycobacterial activity in vitro against *Mycobacterium tuberculosis* $H_{37}R_v$, clinical isolates of *M. tuberculosis* and MDR clinical isolates of *M. tuberculosis* using the proportion test. Lowenstein-Jensen medium is used forthe proportion method. The tubes used are 17 mm in diameterand contain 7 ml of medium. The drugs,dissolved in distilled water, are

incorporated in themedium before coagulation. The control medium without the drug is prepared at the same time as the drug-containing media. After the drug has been added to the medium and after the medium has been distributed in the tubes, the medium is coagulated at 85°C for 50 minutes. The tubes are left at room temperature for 24 hours with cotton-wool plugs and are then covered with rubber caps and put in the refrigerator. The results are read for the first time on the28th day.Second reading was made on the 40th day.MICs of the compounds were reported in Table 1.

Conclusion

The antimicrobial activity of the two new series described here suggests that they may be selectively targeted to M. tuberculosis growths. They were effective in inhibiting M. tuberculosis infection at 40.0 μg/mL concentrations, and could be a good start point to further studies.

Conflict of interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

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