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Discovery of novel antitubercular 2,10-dihydro-4a*H*-chromeno-[3,2-*c*]pyridin-3-yl derivatives

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ABSTRACT

Twenty two novel 2,10-dihydro-4a*H*-chromeno[3,2-*c*]pyridin-3-yl derivatives were synthesized by reacting 3-formyl chromone, (sub)-2-amino pyridines, *N*1-(prop-2-ynyl)arylamides in the presence of indium triflate. The compounds were evaluated their preliminary *in-vitro* and *in-vivo* activity against *Mycobacterium tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB). Among them *N*-[(4a*S*)-2-(3-methyl-2-pyridinyl)-10-oxo-2,10-dihydro-4a*H*-chromeno[3,2-*c*]pyridin-3-yl]methyl-4-ethylbenzenecarboxamide **4d** was found to be the most active compound *in-vitro* with MIC's of 0.22 and 0.07 μg/mL against MTB and MDR-TB respectively. In the *in-vivo* animal model **4d** decreased the bacterial load in lung and spleen tissues with 1.11 and 2.94-log10 protections respectively at 25 mg/kg body weight dose.

1. Introduction

Mycobacterium tuberculosis infections are responsible for one in four avoidable adult deaths in developing countries. While there are a number of effective drugs available for treating tuberculosis (TB), current strategies are greatly complicated by the several months of chemotherapy required to eliminate persistent bacteria. In addition, widespread non-compliance has contributed to the emergence of multidrug-resistant (MDR) and (XDR) TB, extensively drug-resistant strains [1,2]. There is a clear need for fast acting drugs that are capable of eliminating an infection in just a few weeks. In an effort to discover new and effective chemotherapeutic agents for the treatment of tuberculosis, we recently reported the *in-vitro* and *in-vivo* antimycobacterial activity of various thiazolyl thiourea/thiosemicarbazones [3,4], spiro-piperidin-4-ones [5], oxobenzothiazolo[3,2-a]quinoline-6-carboxylic acids [6], thiazeto[3,2-a]quinoline-3-carboxylic acids [7], 8-naphthyridine-3-carboxylic acid [8], 5H-thiazolo[3,2-a]quinoline-4-carboxylic acid [9] and pyrano[3,2-c]pyridine-3-carbonitriles [10]. In the course of screening to discover new antimycobacterial compounds, we identified 2,10-dihydro-4a*H*-chromeno[3,2-*c*]pyridin-3-yl derivatives which inhibited *in-vitro M. tuberculosis H37Rv* (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB). We present herein the preliminary results concerning the synthesis and the *in-vitro* and *in-vivo* antituberculous activity of first representative compound of this family.

2. Synthesis

Microwave-assisted one-pot synthesis of novel 2,10-dihydro-4a*H*-chromeno[3,2-*c*]pyridin-3-yl derivatives was achieved in two steps (Scheme 1). Firstly 3-formyl chromone (**1**) on reaction with 2-amino-3-methyl pyridine/2-amino-3,5-dibromo pyridine (**2a**–**b**) and using catalytic amount of toluene-*p*-sulfonic acid [11] under microwave irradiation (280 w for 1 min) yielded chromone Schiff bases. These imines were prepared in good yields without the formation of any side products arising from Michael-type additions onto the carbon–carbon double bond of the chromone moiety [12]. In the second stage, cycloaddition reaction was carried out by the addition of a catalytic amount of indium triflate to chromone Schiff bases and various *N*1-(prop-2-ynyl)arylamides (**3a**–**k**) in acetonitrile under microwave irradiation (280 w for 4 min) yielded *endo* cycloadducts **4**–**5a**–**k**. When compared to conventional methods [13] which required 85 °C for 4 h and gave 42–78% of cycloadducts, microwave irradiation yielded 68–84% in short reaction time. Compounds *N*1-(prop-2-ynyl)arylamides (**3a**–**k**) were prepared by reacting equimolar concentration of corresponding aryl acid chlorides with propargyl amine in presence of triethylamine in acetonitrile under nitrogen

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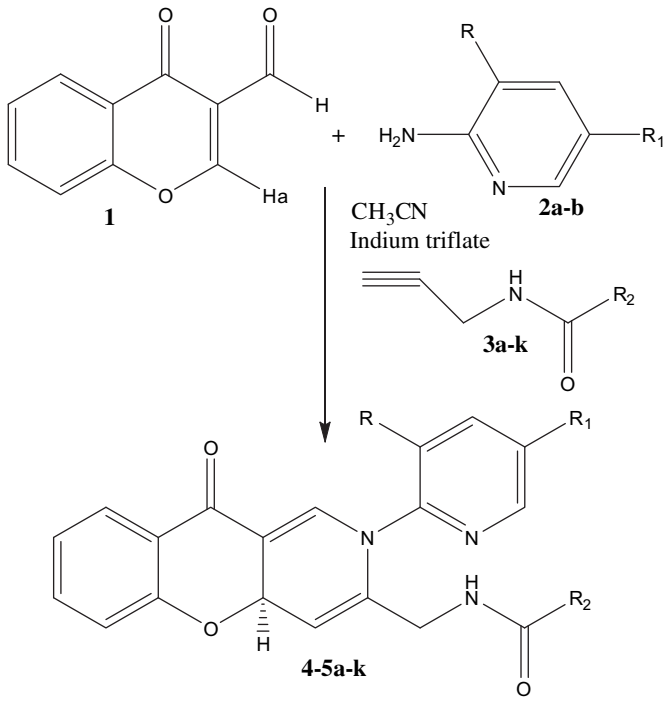


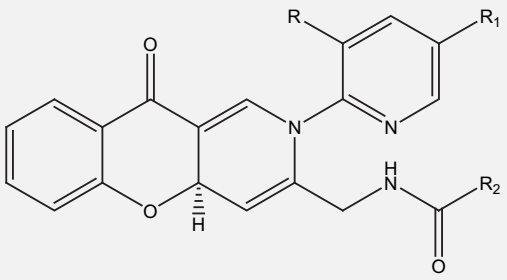
Scheme 1. Synthetic protocol of the compounds.

atmosphere. The structural assignment for the titled compounds as *endo* is based on its high-resolution ^{1}H NMR spectra. The diagnostic signal for the proton H_a in chromone Schiff base, which appeared at δ 8.65, was absent in the titled compounds, whilst the upfield shift of this proton from δ 8.65 to 5.34 showed that cycloaddition had occurred at the C-2 position of the chromone unit, which clearly ruled out the possibility of other product and also there was no evidence for the formation of any *exo* product. The purity of the compounds was checked by TLC and elemental analyses; and the compounds of this study were identified by spectral data.

3. Results and discussion

All compounds were screened for their *in-vitro* antimycobacterial activity against MTB and MDR-TB by agar dilution method similar to that recommended by the National Committee for Clinical Laboratory Standards [14] for the determination of MIC in duplicate. The MDR-TB clinical isolate was obtained from Tuberculosis Research Center, Chennai, India, and was resistant to isoniazid (INH), rifampicin, ethambutol and ofloxacin. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth and MIC's of the synthesized compounds along with the standard drugs for comparison were reported (Table 1). In the first phase of screening against MTB, all the compounds showed excellent *in-vitro* activity against MTB with MIC less than 15 μM. Three compounds (**4d**, **4j** and **4k**) inhibited MTB with MIC of less than 1 μM and compound **4d** (MIC: 0.22) was more potent than standard isoniazid (MIC: 0.36 μM). When compared to ofloxacin (MIC: 2.13 μM), eight compounds (**4b**, **4c**, **4d**, **4e**, **4f**, **4j**, **4k** and **5k**) were found to be more active against MTB. Fifteen compounds were more potent than ethambutol. Compound *N*1-[2-(3-methyl-2-pyridyl)-10-oxo-2,10-dihydro-4a*H*-chromeno[3,2-*c*]pyridin-3-yl]methyl-4-ethylbenzamide (**4d**) was found to be the most active compound *in-vitro* with a low MIC of 0.22 μM against MTB and was 1.6, 9.6 and 34 times more potent than isoniazid, ofloxacin and ethambutol respectively. Subsequently some

Table 1
Physical constants, *in-vitro* antimycobacterial activities and cytotoxicity.



No	R	R_1	R_2	Yield (%)	M.P (°C)	IC_{50} (μM) Vero	MIC (μM) MTB	MIC (μM) MDRTB
4a	CH_3	H	Phenyl	78	118–119	>147.59	7.36	3.68
5a	Br	Br	Phenyl	71	131	NT[a]	11.01	NT
4b	CH_3	H	4-Methylphenyl	83	126	>142.86	1.78	1.78
5b	Br	Br	4-Methylphenyl	76	120–121	NT	5.38	NT
4c	CH_3	H	4-Methoxyphenyl	73	128–129	>137.91	1.72	3.44
5c	Br	Br	4-Methoxyphenyl	84	118	NT	10.46	NT
4d	CH_3	H	4-Ethylphenyl	80	95	>138.42	0.22	0.07
5d	Br	Br	4-Ethylphenyl	79	111–112	104.99	2.6	1.30
4e	CH_3	H	3-Chlorophenyl	70	123–125	>136.48	1.70	1.70
5e	Br	Br	3-Chlorophenyl	72	150	103.87	5.20	2.60
4f	CH_3	H	4-Chlorophenyl	68	137	136.49	1.70	3.40
5f	Br	Br	4-Chlorophenyl	69	127–129	>103.87	2.95	2.95
4g	CH_3	H	3,4-Dichlorophenyl	70	154–155	NT	12.69	NT
5g	Br	Br	3,4-Dichlorophenyl	67	159	50.69	9.82	4.91
4h	CH_3	H	4-Fluorophenyl	73	136	>141.61	7.09	7.09
5h	Br	Br	4-Fluorophenyl	70	121–122	NT	10.67	NT
4i	CH_3	H	Phenoxymethyl	79	103–105	NT	13.78	NT
5i	Br	Br	Phenoxymethyl	74	141	NT	10.46	NT
4j	CH_3	H	2-Naphthyl	84	149	141.67	0.84	0.42
5j	Br	Br	2-Naphthyl	80	138–139	101.24	2.52	5.04
4k	CH_3	H	7-Methylnaphth-2-yl	76	147–148	>128.19	0.41	0.13
5k	Br	Br	7-Methylnaphth-2-yl	80	110	99.00	1.23	0.61
INH	–	–	–	–	–	>455.8	0.36	45.57
Rifamp	–	–	–	–	–	>75.94	0.12	3.79
Oflox	–	–	–	–	–	>155.3	2.13	34.59
Etamb	–	–	–	–	–	>305.90	7.63	122.36

[a] Not tested.

of the compounds were evaluated against MDR-TB, and among the fifteen compounds screened, all the compounds inhibited MDR-TB with MIC ranging from 0.07 to 7.09 μM and were found to be more active than isoniazid (MIC: 45.57 μM), ofloxacin (MIC: 34.39 μM) and ethambutol (MIC: 122.36 μM). Four compounds (**4d**, **4j**, **4k** and **5k**) inhibited MDR-TB with MIC of less than 1 μM; and compound **4d** endowed with high activity toward MDR-TB. Compound **4d** was found to be the most active compound *in-vitro* with MIC of 0.07 μM against MDR-TB and was 651, 54, 494 and 1748 times more potent than isoniazid, rifampicin, ofloxacin and ethambutol respectively. With respect to structure–MTB activity relationship, the results demonstrated that the antimycobacterial activity was enhanced by the introduction of electron donating methyl group in the pyridyl moiety (**4a**–**k**), whereas introduction of weakly deactivating electron withdrawing dibromo groups (**5a**–**k**) decreased the activity. Similar

types of results were found with respect to substitution on the phenyl ring wherein electron donating methyl, ethyl and methoxy groups showed good activity. Substitution with halogen(s) decreased the activity considerably. Replacement of phenyl ring with naphthyl moiety enhanced the activity 4–8 times (**4a**,**5a** Vs **4j**,**5j**), and further introduction of methyl group in naphthyl moiety enhanced the activity two times (**4j**,**5j** Vs **4k**,**5k**). Replacement of phenyl ring with phenoxymethyl group was detrimental to activity.

Some compounds were further examined for toxicity (IC_{50}) in a mammalian Vero cell line till 62.5 μg/mL concentrations by serial double dilution technique [15]. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product and the results are reported in Table 1. Fifteen compounds when tested showed IC_{50} values ranging from 50.69 to >147.6 μM. A comparison of the substitution pattern at pyridyl ring demonstrated that 3,5-dibromo-2-pyridyl derivatives were more cytotoxic than the 3-methyl-2-pyridyl derivatives. These results are important as the 3,5-dibromo-2-pyridyl substituted compounds with their increased cytoliability, are much less attractive in the development of a compound for the treatment of TB. This is primarily due to the fact that the eradication of TB requires a lengthy course of treatment, and the need for an agent with a high margin of safety becomes a primary concern. The compound **4d** was found to be non-toxic up to 62.5 μg/mL (>138.42 μM) and showed selectivity index (IC_{50}/MIC) of more than 629 for MTB and 1977 for MDR-TB.

Subsequently, compound **4d** was tested for *in-vivo* efficacy against MTB at a dose of 25 mg/kg (Table 2) in CD-1 mice [16]. The mice were infected intravenously with *M. tuberculosis* ATCC 35801. Drug treatment by intra-peritoneal route began after 10 days of inoculation of the animal with microorganism and continued for 10 days. After 35 days post infection the spleens and right lungs were aseptically removed, and the number of viable organisms was determined and compared with the counts from negative (vehicle treated) controls (Mean culture forming units (CFU) in lung: 7.99 ± 0.16 and in spleen: 9.02 ± 0.21). Compound **4d** decreased the bacterial load in lung and spleen tissues with 1.11 and 2.94-log10 protections respectively and was considered to be promising in reducing bacterial count in lung and spleen tissues. When compared to isoniazid at the same dose level **4d** was found to be less active in the *in-vivo* study.

Screening of the antimycobacterial activity of these novel series, identified 2,10-dihydro-4a*H*-chromeno[3,2-*c*]pyridin-3-yl derivatives as a new lead endowed with antitubercular activity, exhibiting MIC values between 0.22 and 13.78 μM. In conclusion, it has been shown that the potency, selectivity, and low cytotoxicity of these compounds make them valid leads for synthesizing new compounds that possess better activity. Further structure–activity and mechanistic studies should prove fruitful.

4. Experimental protocols

4.1. Chemistry

Melting points were taken on an electrothermal melting point apparatus (Buchi BM530) in open capillary tubes and are uncorrected ^{1}H NMR spectra were scanned on a JEOL Fx 400 MHz NMR spectrometer using DMSO-d_6 as solvent. Chemical shifts are expressed in δ (ppm) relative to tetramethylsilane. Elemental analyses (C, H, and N) were performed on Perkin Elmer model 240C analyzer and the data were within ±0.4% of the theoretical values.

Table 2
In vivo activity of **4d** and isoniazid against *M. tuberculosis* ATCC 35801 in mice.

Compound	Lungs (log CFU ± SEM)	Spleen (log CFU ± SEM)
Control	7.99 ± 0.16	9.02 ± 0.21
Isoniazid (25 mg/kg)	5.86 ± 0.23	4.71 ± 0.10
4d (25 mg/kg)	6.88 ± 0.17	6.08 ± 0.13

4.1.1. General procedure for the synthesis of 2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl derivatives (**4**–**5a**–**k**)

Toluene-*p*-sulphonic acid (10 mg) was added to a solution of 3-formyl chromone (**1**) (1 equival.) and corresponding 2-amino-3-methyl pyridine/2-amino-3,5-dibromo pyridine (**2a**–**b**) (1 equival.) in acetonitrile and the resulting mixture was kept under microwave irradiation (280 w for 1 min). After that without separation of compound, Indium triflate (1 equival.) and *N*1-(prop-2-ynyl)-arylamides (**3a**–**k**) was added and the resulting mixture was kept under microwave irradiation (280 w for 4 min). After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure yielded the products **4**–**5a**–**k**.

4.1.2. N-[(4aS)-2-(3-methyl-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methylbenzenecarboxamide (**4a**)

Yield: 78%; m.p: 118–119 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 2.05 (s, 3H), 4.30 (dd, 2H), 5.10 (m, 1H), 5.7 (d, 1H), 6.2 (s, 1H, D_2O exchangeable), 6.68 (q, 1H), 7.02–8.18 (m, 12H); Anal ($C_{26}H_{21}N_3O_3$) C, H, N.

4.1.3. N-[(4aS)-2-(3,5-dibromo-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methyl-4-methylbenzenecarboxamide (**5b**)

Yield: 76%; m.p: 128–129 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 2.32 (s, 3H), 4.30 (dd, 2H), 5.09 (m, 1H), 5.72 (d, 1H), 6.25 (s, 1H, D_2O exchangeable), 6.68 (q, 1H), 7.04–8.10 (m, 10H); Anal ($C_{26}H_{19}Br_2N_3O_3$) C, H, N.

4.1.4. N-[(4aS)-2-(3-methyl-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methyl-4-methoxybenzenecarboxamide (**4c**)

Yield: 73%; m.p: 120–121 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 2.05 (s, 3H), 3.8 (s, 3H), 4.31 (dd, 2H), 5.1 (m, 1H), 5.72 (d, 1H), 6.25 (s, 1H, D_2O exchangeable), 6.64 (q, 1H), 7.02–8.18 (m, 11H); Anal ($C_{27}H_{23}N_3O_4$) C, H, N.

4.1.5. N-[(4aS)-2-(3,5-dibromo-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methyl-4-ethylbenzenecarboxamide (**5d**)

Yield: 79%; m.p: 111–112 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.16 (t, 3H), 2.48 (q, 2H), 4.30 (dd, 2H), 5.09 (m, 1H), 5.72 (d, 1H), 6.25 (s, 1H, D_2O exchangeable), 6.68 (q, 1H), 7.02–8.10 (m, 11H); Anal ($C_{27}H_{21}Br_2N_3O_3$) C, H, N.

4.1.6. N-[(4aS)-2-(3-methyl-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methyl-3-chlorobenzenecarboxamide (**4e**)

Yield: 70%; m.p: 123–125 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 2.05 (s, 3H), 4.30 (dd, 2H), 5.09 (m, 1H), 5.72 (d, 1H), 6.25 (s, 1H, D_2O exchangeable), 6.64 (q, 1H), 7.02–8.18 (m, 11H); Anal ($C_{26}H_{20}ClN_3O_3$) C, H, N.

4.1.7. N-[(4aS)-2-(3,5-dibromo-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methyl-4-chlorobenzenecarboxamide (**5f**)

Yield: 69%; m.p: 127–129 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 4.31 (dd, 2H), 5.12 (m, 1H), 5.72 (d, 1H), 6.25 (s, 1H, D_2O exchangeable), 7.02 (q, 1H), 7.42–8.10 (m, 10H); Anal ($C_{25}H_{16}Br_2ClN_3O_3$) C, H, N.

*4.1.8. N-[(4aS)-2-(3-methyl-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methyl-2,4-dichlorobenzenecarboxamide (**4g**)*

Yield: 70%; m.p: 154–155 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (s, 3H), 4.30 (dd, 2H), 5.09 (m, 1H), 5.72 (d, 1H), 6.25 (s, 1H, D_2O exchangeable), 6.64 (q, 1H), 7.02–8.18 (m, 10H); Anal ($C_{26}H_{19}Cl_2N_3O_3$) C, H, N.

*4.1.9. N-[(4aS)-2-(3,5-dibromo-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methyl-4-fluorobenzenecarboxamide (**5h**)*

Yield: 70%; m.p: 121–122 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 4.30 (dd, 2H), 5.09 (m, 1H), 5.72 (d, 1H), 6.25 (s, 1H, D_2O exchangeable), 7.02 (q, 1H), 7.46–8.10 (m, 10H); Anal ($C_{25}H_{16}Br_2FN_3O_3$) C, H, N.

*4.1.10. N-[(4aS)-2-(3-methyl-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methyl-2-phenoxyacetamide (**4i**)*

Yield: 79%; m.p: 103–105 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (s, 3H), 4.30 (dd, 2H), 4.61 (s, 2H), 5.39 (m, 1H), 5.72 (d, 1H), 6.62–6.68 (m, 5H), 7.02–8.19 (m, 9H); Anal ($C_{27}H_{23}N_3O_4$) C, H, N.

*4.1.11. N-[(4aS)-2-(3,5-dibromo-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methyl-2-naphthamide (**5j**)*

Yield: 80%; m.p: 138–139 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 4.31 (dd, 2H), 5.1 (m, 1H), 5.72 (d, 1H), 6.25 (s, 1H, D_2O exchangeable), 7.02 (q, 1H), 7.2–8.10 (m, 13H); Anal ($C_{29}H_{19}Br_2N_3O_3$) C, H, N.

*4.1.12. N-[(4aS)-2-(3-methyl-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl]methyl-7-methyl-2-naphthamide (**4k**)*

Yield: 76%; m.p: 147–148 °C; ^{1}H NMR (DMSO-d_6) δ ppm: 2.06 (s, 3H), 2.37 (s, 3H), 4.30 (dd, 2H), 5.09 (m, 1H), 5.72 (d, 1H), 6.25 (s, 1H, D_2O exchangeable), 6.64 (m, 1H), 7.02 (m, 1H), 7.23–8.37 (m, 12H); Anal ($C_{31}H_{25}N_3O_3$) C, H, N.

4.2. In-vitro antimycobacterial activity

All compounds were screened for their *in-vitro* antimycobacterial activity against MTB, MDR-TB and MC^2 in Middlebrook 7H11agar medium supplemented with OADC by agar dilution method similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in duplicate. The MDR-TB clinical isolate was obtained from Tuberculosis Research Center, Chennai, India, and was resistant to isoniazid, rifampicin, ethambutol and ofloxacin. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth.

4.3. Cytotoxicity

Some compounds were further examined for toxicity (IC_{50}) in a mammalian Vero cell line at concentrations of 62.5 μg/mL. After 72 h of exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 non-radioactive cell proliferation assay.

4.4. In-vivo antimycobacterial activity

One compound was tested for efficacy against MTB at a dose of 25 mg/kg in six-week-old female CD-1 mice six per group. In this model, the mice were infected intravenously through caudal vein approximately 10^7 viable *M. tuberculosis* ATCC 35801. Drug treatment by intra peritoneal route began after 10 days of inoculation of the animal with microorganism and continued for 10 days. After 35 days post infection the spleens and right lungs were aseptically removed and ground in a tissue homogenizer, the number of viable organisms was determined by serial 10-fold dilutions and subsequent inoculation onto 7H10 agar plates. Cultures were incubated at 37 °C in ambient air for 4 weeks prior to counting. Bacterial counts were measured, and compared with the counts from negative controls (vehicle treated) in lung and in spleen.

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