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Antibacterial activity of new substituted 4-*N*-alkylated-2-trifluoromethyl-quinoline analogues against sensitive and resistant *Mycobacterium tuberculosis* strains

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ABSTRACTS

Objectives: The emergence of resistant strain has aggravated the tuberculosis situation in the world, running out of control and hard to fight. We evaluate forty new quinoline analogues against sensitive and resistant *Mycobacterium tuberculosis* (*Mtb*).

Methods: The compounds were obtained via synthesis and evaluated against sensitive strain ATCC 27294. Selected compounds were evaluated against resistant strains SR 2571/0215 and T113/09, using the MABA method. The more active compounds were selected for their potential cytotoxic activity against human macrophage cells.

Results: Twenty-nine compounds displayed activity against sensitive strain, and thirteen were active against resistant strains. Against sensitive strain, the most promising compounds were **4c** and **4d** (MIC = 9 and 12 μM, respectively). Against resistant strains, the compounds **4a, 4d** displayed the best results (MIC = 4 and 5 μM, respectively). The active compounds **4a, 4d, 6d, 7c, 8d**, and **10d** were non-cytotoxic to the host cells at concentrations near to the MIC. The non-cytotoxic compound **4d** was the most potent against resistant and sensitive *Mtb*.

Conclusion: These findings contribute to relevant information and perspectives in search of new bioactive compounds against sensitive and resistant TB. Resistant strains have turned tuberculosis a severe disease in the world.

1. Introduction

Quinoline or benzo[b]pyridine is chemically a weak base and was discovered by Friedlieb Rouge in 1834 as a colorless hygroscopic liquid, through of the distillation of coal tar (Nainwal et al., 2019). The quinoline nucleus is one of the essential heterocycles in the fields of drug discovery (Musiol et al., 2017; Shang et al., 2018; Fourmet et al., 1994; Narwal et al., 2017; Sharma et al., 2017; Chokkar et al., 2019). Due to its importance, several methodologies for obtaining have been described in the literature (Nainwal et al., 2019; Ramann and Cowen, 2016; Sharma et al., 2018). The quinoline nucleus is considered a privileged scaffold (Zhao and Dietrich, 2015) since it can bind more than one receptor, mainly has been explored in search of new bioactive compounds. This class has promising perspectives as anti-tuberculosis agent (Singh et al., 2015; Keri and Patil, 2014; Liu et al., 2018).

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* (*Mtb*), being a serious public health problem worldwide, affecting one-third of the world population and still causing the death of thousands of people (World Heath Organization, 2020). It is transmitted through the air and mainly affects the lungs. The emergence of resistant strain has aggravated the TB situation in the world, running out of control and hard to fight (WHO, 2020). TB Bacterial strains have been classified into three types: MDR-TB, multidrug-resistant, defined as resistance to isoniazid and rifampicin; XDR-TB, extensively drug-resistant, defined as resistance to at least isoniazid and rifampicin, and to any fluoroquinolone, and any of the three second-line injectable drugs

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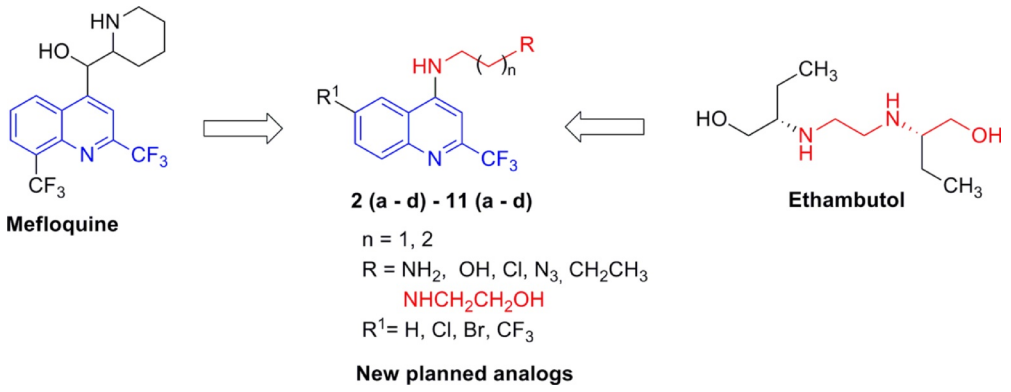
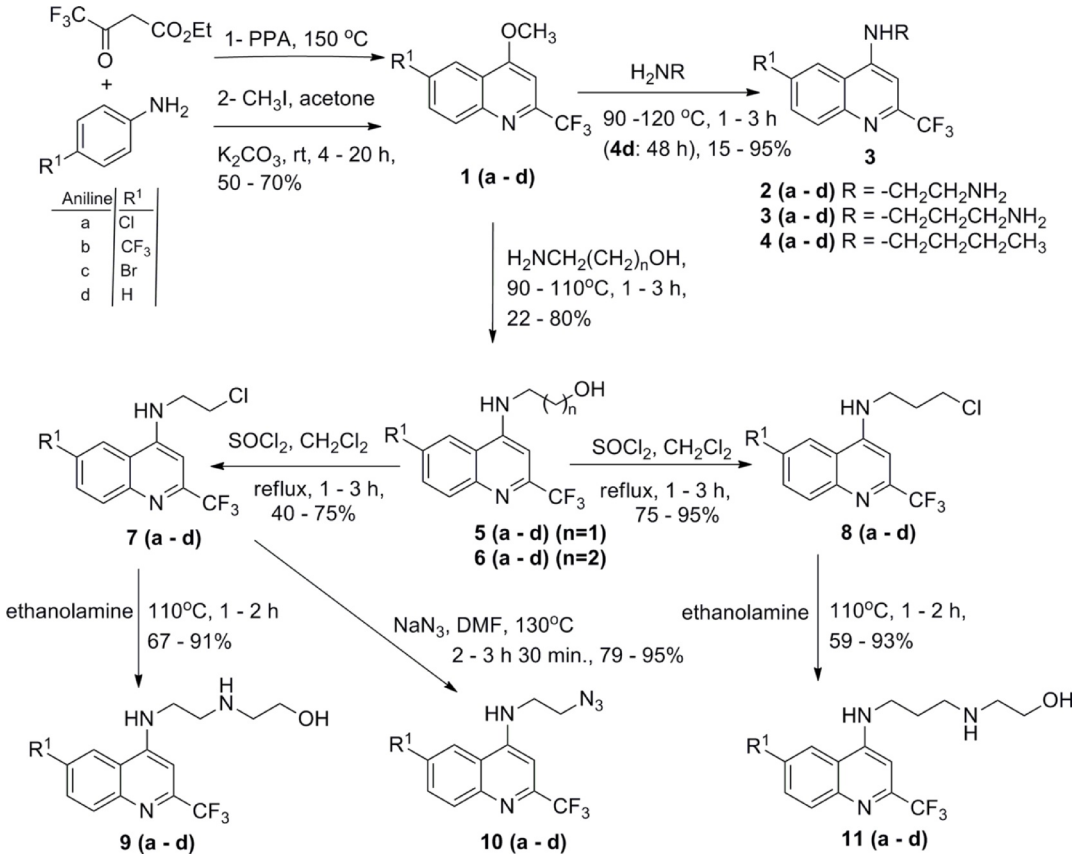


Figure 1. New planned quinoline analogues 2 (a – d) – 11 (a – d).



Scheme 1. Synthetic route for obtaining of substituted 4-*N*-alkylated-2- trifluoromethyl-quinoline analogues.

(amikacin, capreomycin, and kanamycin), and TDR-TB, totally drug-resistant, defined as resistance to all first-line anti-TB drugs and second-line anti-TB drugs (WHO, 2020). In the last 50 years, only two new drugs have been approved by FDA for the treatment of resistant tuberculosis, Bedaquiline and Delamanid in 2012 and 2014, respectively, and few studies advance to the clinical trials (Leea et al., 2019). Nowadays, a new fixed-dose combination was developed using the drug Pretomanid, which was developed by TB Alliance (TB Alliance, 2019). This combination employed the use of three drugs, Bedaquiline, Pretomanid, and Linezolid for the treatment of XDR-TB or treatment-intolerant/non-responsive MDR-TB. The result of this treatment is a success of over 90% after six months in select patients (TB Alliance, 2019). However, this treatment displays various limitations as side effects that require monitoring of the individual's health conditions. The need for alternative and more effective treatments is still pressing.

Due to our experience in search of new TB bioactive compounds based on the quinoline nucleus (Araújo et al., 2019; Gonçalves et al., 2012), we proposed in this present work the synthesis and biological evaluation of new derivatives **2** (**a** – **d**) – **11** (**a** – **d**) (Figure 1). These new analogues were planned based on molecular hybridization between Mefloquine, a known compound active against sensitive and resistant strains of *Mtb*, and Ethambutol, a first-line drug used in the treatment of non-complicated tuberculosis (Figure 2). Compounds containing quinoline and quinolone nucleus in general show mechanism of action by inhibition of DNA gyrase or ATP synthase. DNA gyrase, a crucial enzyme in DNA metabolism, is a validated good potential target to develop potent and safer lead compounds as this enzyme is absent in eukaryotic cells. ATP synthase (ATPase) is a very complex enzyme that directly generates adenosine triphosphate (ATP). Thus, if ATPase enzyme is inhibited, the bacterium is deprived of energy that causes it to die. Ethambutol is a strong inhibitor of cell wall

synthesis by inhibition of aranbinosyltransferase. Due to this Arabinan, a component of arabinogalactan that constitue the cell wall, is not generated (Villamizar-Mogotocoro et al., 2020).

The pharmacophore amino alcohol group of the Ethambutol was introduced at 4-position of the quinoline ring (group in red, Figure 1, n = 1, R = $NHCH_2CH_2OH$), as well as of similar (n = 2, R = $NHCH_2CH_2OH$) and simplified groups (R = NH_2, OH), including groups with lipophilic characteristics (R = CH_2CH_3, Cl, N_3). Modifications on the quinoline ring were promoted, with the insertion of lipophilic substituents (R^1 = Cl, Br) and the exchange position of the trifluoromethyl group (Figure 1, R^1 = CF_3). The absence of substituents on the quinoline ring, as well as the induction effect of electron-donating and electron-withdrawing groups, were also evaluated. The use of bromo at 6-position of the quinoline ring was motivated by Bedaquiline, which present this atom in this position (Hards et al., 2015).

2. Results and discussion

2.1. Chemistry

For the synthesis of the new analogues **2** (**a** – **d**) - **11** (**a** – **d**, Scheme 1), we used the synthetic methodology previously described by our group (Araújo et al., 2019). The first step reaction is the formation of the quinoline nucleus, based on the condensation reaction with different anilines with PPA at 150°C for 2-3 hours. The formed nucleus possessed at 6-position, chloro, trifluoromethyl, bromo and hydrogen, and also a free hydroxyl group at 4-position. This hydroxyl group was then alkylated using methyl iodide to form a leaving group, which will react with nucleophiles. Methylation was made by using methyl iodide in acetone at room temperature in the presence of Na_2CO_3, for 4 – 20 hours, to furnish the compounds **1** (**a** – **d**) in 50 – 70% yield. These compounds reacted with diamines, butylamine, and amino alcohols at 90 – 120°C to furnish the derivatives **2** (**a** – **d**), **3** (**a** – **d**), **4** (**a** – **d**), **5** (**a** – **d**), and **6** (**a** – **d**) in 15-95% yield after 1-3 hours (**4d**: 48 h). The compounds **5** (**a** – **d**) and **6** (**a** – **d**) were converted to chloro derivatives **7** (**a** – **d**) and **8** (**a** – **d**) by treatment with $SOCl_2$ in CH_2Cl_2 or $CHCl_3$ at reflux in 40 – 95% yield after 1-3 hours of reaction (Scheme 1).

The compounds **9** (**a** – **d**) were obtained after reaction of **7** (**a** – **d**) with ethanolamine under heating at 110°C for 1-2 hours in 67 – 91% yield. The azido compounds **10** (**a** – **d**) were obtained after reaction of **7** (**a** – **d**) with sodium azide in DMF at 130°C for 2 – 3.5 hours in 79 – 95% yield. The compounds **11** (**a** – **d**) were obtained after reaction of **8** (**a** – **d**) with ethanolamine at 110°C for 1-2 hours in 59 – 93% yield.

All these new compounds were identified by detailed spectral data, including ^{1}H NMR, ^{13}C NMR, and high resolution mass spectra. In general, the ^{1}H NMR spectrum showed four or five quinoline protons at 8.90 – 6.20 ppm and the aliphatic protons at 4.00 – 0.95 ppm. The ^{13}C NMR spectrum showed the quinoline carbons signals at the region of 92.84 – 164.52 ppm and the aliphatic carbons at the regions of 13.64 – 60.49 ppm. The CF_3 group showed a quartet with *J* about 270-274 Hz. In the IR spectra, characteristic signals of NH were observed at 3200 – 3380 cm^{-1}, OH were observed at 3500 – 4000 cm^{-1}, and N_3 were observed at 2090 – 2100 cm^{-1}. In all compounds were observed for the C-F axial deformation signals at 1080 – 1300 cm^{-1}.

2.2. Antimycobacterial activity against M. tuberculosis H37Rv (ATCC 27294)

The antimycobacterial activities of derivatives **2** (**a** – **d**) – **11** (**a** – **d**), showed in Table 1, were assessed against *M. tuberculosis* H37Rv (ATCC 27294) using the microplate Alamar Blue assay (MABA) (Franzblau et al., 1998).

Of these forty planned and synthesized compounds, twenty-nine exhibited activity with MIC values of 9 to 392 μM (Table 1). In general, compounds possessing lipophilic groups at the 4-position of the quinoline ring **4** (**a** – **d**), **7** (**a, c, d**), **8** (**a** – **d**), and **10** (**a** – **d**) (9 – 182 μM), were the more actives. However, the exception is **6d** with activity of 93 μM. The azide derivatives **10** (**a - d**) presented reasonable activity (44 – 143 μM) with low log P values. Compounds substituted with butyl groups at the position 4 of the quinoline ring **4** (**a, c, d**) (9 – 41 μM) were more actives than the compounds **2** (**a** – **d**), **3** (**a** – **d**), **5** (**a -d**), **6** (**a** – **d**), **7** (**a, b, d**), **8b, 9** (**a** – **d**), **10** (**a** – **d**), and **11** (**a** – **d**) (≥ 44 μM). The amino alcohol group present in Ethambutol at the 4-position, **9** (**a** – **d**), as well as of similar group, **11** (**a** – **c**), and simplified groups, **2** (**a, c, d**), **3c, 5d**, and **6b**, displayed moderated activity (150 – 392 μM). The compounds **2b, 3a, 3b, 3d, 5** (**a** – **c**), **6a, 6c, 7b** and **11d** were inactive.

Analyzing only the substituents at 6-position, the CF_3 group seems to impair the activity concerning to others evaluated substituents despite it confer the highest lipophilicity according to values log P (Table 1). It assumes that property electron-withdrawing of the CF_3 group in this position affect the activity. In general, the bromo substituent resulted in more actives compounds. However, unsubstituted compounds showed interesting similar activity and, in some cases, were more actives (**6d** vs. **6c**, **8d** vs. **8c, 10d** vs. **10c**). The majority of the compounds substituted with chloro group not were more actives than the corresponding unsubstituted.

As done in the previous work (Araújo et al., 2019), the more active compounds against sensitive strain (13 compounds) were evaluated against resistant strains (SR2571/0215; T113/09 strains resistant to Rifampicin and Isoniazid) and are demonstrated in Table 2. Nine compounds displayed higher activity to resistant strains (lower MIC value) than to sensitive strain. The compound **4a** with activity at 41 μM showed excellent activity against resistant strain at 4 μM. Compound **4d** with activity at 12 μM displayed activity against resistant strain at 5 μM. The compound **10d** was also much more active to resistant strain (11 μM) than to sensitive strain (44 μM; Table 2). A hypothesis raised by us is that activity of these new analogues was believed to be through a different mechanism of action, or more than one, perhaps similar to that presented by Mefloquine, which is like that of Bedaquiline (Hards et al., 2015). This latter presents its antimycobacterial action by inhibiting the enzyme F1Fo-ATP synthase, causing the death of even non-replicating cells.

The more active compounds in sensitive and resistant strains were assayed to cellular viability in the presence and absence of test compounds by Mosmans's MTT (3-(4,5-demethylthylthiazol-2-yl)-2,5-dimethyl tetrazolium bromide; Merck) microcultured tetrazolium assay, utilizing human macrophages cells (Mosmann, 1983). The results were expressed as percentage cell viability in different concentrations: 1, 10, 100, and 1000 μM (Table 3). The more active compounds to resistant strains **4a, 4d, 7c, 8d,** and **10d** were not cytotoxic to the host cells at concentrations near the MIC. The more active compounds to sensitive strain **4d, 6d, 8d**, and **10d** also were not cytotoxic to the host cells at concentrations near the MIC.

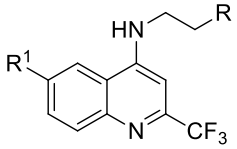
3. Material and methods

All experimental procedures for synthesis and characterization of all substances described are in supporting information.

3.1. Biological Evaluation against Mycobacterium tuberculosis

The antimycobacterial activities of all tested compounds were assessed against sensitive *M. tuberculosis* strain H37Rv (ATCC 27294) and resistant *M. tuberculosis* strain SR571/0215 and T113/09 (resistant to Isoniazid and Rifampicin, no clinical strains), using the microplate Alamar Blue assay (MABA, Tables 1 and 2) (Franzblau et al., 1998) and performed in duplicate. Briefly, 200 microliters of sterile deionized water were added to all outer-perimeter wells of sterile 96-well plates (Falcon, 3072: Becton Dickinson, Lincoln Park, NJ, USA) to minimize evaporation of the medium in the test wells during incubation. The 96 plates received 100 μL of the Middlebrook 7H9 broth (Difco

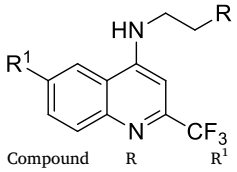
Table 1
Activity of synthesized compounds 2 (a – d) – 11 (a – d) against drug- susceptible H37Rv strain



Compound	R	R^1	C LogP	MIC H37Rv (μM)	Compound	R	R^1	C LogP	MIC H37Rv (μM)
2a	NH_2	Cl	2.21	**346**	7a	Cl	Cl	3.77	81
2b	NH_2	CF_3	2.45	**Res**	7b	Cl	CF_3	4.01	Res
2c	NH_2	Br	2.33	**150**	7c	Cl	Br	3.89	35
2d	NH_2	H	1.61	**392**	7d	Cl	H	3.16	182
3a	CH_2NH_2	Cl	2.67	**Res**	8a	CH_2Cl	Cl	4.22	39
3b	CH_2NH_2	CF_3	2.91	**Res**	8b	CH_2Cl	CF_3	4.46	70
3c	CH_2NH_2	Br	2.79	**287**	8c	CH_2Cl	Br	4.34	34
3d	CH_2NH_2	H	2.06	**Res**	8d	CH_2Cl	H	3.61	22
4a	CH_2CH_3	Cl	4.45	**41**	9a	$NHCH_2CH_2OH$	Cl	2.04	300
4b	CH_2CH_3	CF_3	4.69	**149**	9b	$NHCH_2CH_2OH$	CF_3	2.29	272
4c	CH_2CH_3	Br	4.57	**9**	9c	$NHCH_2CH_2OH$	Br	2.16	265
4d	CH_2CH_3	H	3.84	**12**	9d	$NHCH_2CH_2OH$	H	1.44	334
5a	OH	Cl	2.61	**Res**	10a	N_3	Cl	2.84	79
5b	OH	CF_3	2.85	**Res**	10b	N_3	CF_3	3.08	143
5c	OH	Br	2.73	**Res**	10c	N_3	Br	2.96	69
5d	OH	H	2.00	**391**	10d	N_3	H	2.24	44
6a	CH_2OH	Cl	3.06	**Res**	11a	$CH_2NHCH_2CH_2OH$	Cl	2.50	288
6b	CH_2OH	CF_3	3.31	**296**	11b	$CH_2NHCH_2CH_2OH$	CF_3	2.74	262
6c	CH_2OH	Br	3.18	**Res**	11c	$CH_2NHCH_2CH_2OH$	Br	2.62	255
6d	CH_2OH	H	2.46	**93**	11d	$CH_2NHCH_2CH_2OH$	H	1.89	Res
Ethambutol				**11.3**	**Mefloquine**				30

Compounds **1** (**a** – **d**) not were actives in this essay Res: Resistant at 100 μg/mL

Table 2
Activity of the more actives compounds against resistant *Mtb* (SR571/0215, T113/09)



Compound	R	R^1	MIC (μM) Sensitive strain (ATCC 27294)	MIC (μM) Resistant strain (SR 2571/0215)
4a	CH_2CH_3	Cl	41	4
4c	CH_2CH_3	Br	9	7*
4d	CH_2CH_3	H	12	5*
6d	CH_2OH	H	93	185*
7a	Cl	Cl	81	161
7c	Cl	Br	35	35*
8a	CH_2Cl	Cl	39	19*
8b	CH_2Cl	CF_3	70	35*
8c	CH_2Cl	Br	34	17*
8d	CH_2Cl	H	22	11*
10a	N_3	Cl	79	79
10c	N_3	Br	69	18*
10d	N_3	H	44	11*
Ethambutol	-	-	11.3	61.2
Mefloquine	-	-	30	30

*T113/09 strain.

Laboratories, Detroit, MI, USA) and a serial dilution of the tested compounds **1** (**a** – **d**) – **11** (**a** – **d**) (DMSO) was made directly on the plate. The final concentrations tested were 3.12 to 100.0 μg/mL. Plates were covered and sealed with parafilm and incubated at 37°C for five days. After this time, 25 microliters of a freshly prepared 1:1 mixture of Alamar Blue (Accumed International, Westlake, OH, USA) reagent and 10% Tween 80 were added to the plate and incubated for 24 h. Blue color in the well was interpreted as no bacterial growth, and a pink color was scored as growth. The MIC was defined as the lowest compound concentration, which prevented a color change from blue to pink.

Table 3,
Cytotoxicity of the more actives compounds against sensitive and resistant *Mtb* (Human Macrophages cells)

Compounds	MIC (μM) sensitive strain	MIC (μM) resistant strain	% Cell viability/doses			
			1 μM	10 μM	100 μM	1000 μM
4a	41	4	106.5	80.7	53.1	24.9
4c	9	7	105.8	75.9	52.5	24.9
4d	12	5	108.62	106.1	73.7	58.3
6d	93	185	109.7	104.3	95.9	63.6
7a	81	161	110	100.9	67.7	50
7c	35	35	105	103.9	75.1	32.3
8a	39	19	100	76,3	63,7	54.7
8b	70	35	100.6	98.4	70.2	51.6
8c	34	17	95	81.1	83.4	66.2
8d	22	14	109.5	105.7	81	84.5
10a	79	79	99.2	103.1	74.1	59.7
10c	69	18	106.2	92.52	69.7	56.8
10d	44	14	105	109.5	90.5	72.2

3.2. Cell Viability Assay

Cellular viability in the presence and absence of test compounds was determined by Mosmans´s MTT (3-(4,5-dimethylthiazol-2yl)-2,5-phenyltetrazolium bromide; Merck) microcultured tetrazolium assay (Mosmann, 1983). The cells were plated in flat bottom 96-well plates (2.5 × 106 cells/mL) cultured for 1 h in a controlled atmosphere (CO_2 5% at 37 °C), and non-adherent cells were washed by gentle flushing with RPMI1640. Adherent cells were cultured in the presence of medium alone, tween 20 (3%) (live and dead controls, respectively) or different concentrations of compounds (Table 3; 1, 10, 100, 1000 μM) in a triplicate assay. After 18 h, stock MTT solution (5 mg/mL of saline; 20 μL/well) was added to the culture, and 4 h later, supernatant was discharged, and DMSO (100 μL/well) was added for formazan crystals

solubilization, and the absorbance was read at 540 nm in a plate reader (Biorad-450).

4. Conclusion

Twenty-nine compounds showed some activity to the sensitive strain, being the highest active **4c** and **4d** similar to Ethambutol, the drug of reference. Thirteen compounds in this series were also evaluated against resistant strains (resistant to Rifampicin and Isoniazid), displaying all some activity. Incredibly, some these displayed lower MIC values, with the compounds **4a**, **4d** the highest active against resistant strains. The more active compounds to resistant strains **4a**, **4d**, **7c**, **8d**, and **10d** were not cytotoxic to the host cells at concentrations near the MIC, as well as the more active compounds to sensitive strains **4d**, **6d**, **8d**, and **10d.** The non-cytotoxic compound **4d** was the most potent against resistant and sensitive Mtb in this series. These findings contribute to relevant information and perspectives in search of new bioactive compounds against sensitive and resistant TB.

CRediT authorship contribution statement

Emerson Teixeira da Silva: Conceptualization, Data curation, Investigation, Methodology, Resources, Visualization, Writing - original draft, Writing - review & editing. **Gabriel Fernandes de Andrade:** Formal analysis, Investigation, Resources, Visualization. **Adriele da Silva Araújo:** Formal analysis, Investigation, Resources. **Maria Cristina Silva Lourenço:** Data curation, Formal analysis, Methodology, Resources, Validation. **Marcus Vinícius Nora de Souza:** Visualization, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2020.105596.

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