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Synthesis, tuberculosis inhibitory activity, and SAR study of N-substituted-phenyl-1,2,3-triazole derivatives

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Abstract—The aim of this work was to describe the synthesis, the in vitro anti-*Mycobacterium tuberculosis* profile, and the structure–activity relationship (SAR) study of new N-substituted-phenyl-1,2,3-triazole-4-carbaldehydes (**3a–l**). The reactions of aromatic amine hydrochlorides with diazomalonaldehyde (**1**) produced several N-substituted-phenyl-1,2,3-triazole-4-carbaldehydes (**3a–l**) in moderate-to-good yields. In order to investigate the influence of the difluoromethylene group on the anti-*Mycobacterium* activity of these compounds, fluorination of triazoles with DAST converted the corresponding carbaldehyde compounds into new difluoromethyl derivatives (**4a–l**) in excellent yield. Characterization of all compounds was achieved by spectroscopic means and additional for 1-(4-methylphenyl)-1,2,3-triazole-4-carbaldehyde, **3k** by X-ray crystallography. Compounds (**3a–l**) and (**4a–l**) have been screened for the inhibitory activity against *Mycobacterium tuberculosis* H37Rv strain (ATCC 27294) and all of them were able to inhibit the growth of the bacterium. Interestingly, **3a** and **3k** exhibited the best inhibition with MIC values of 2.5 μg/mL, similar to pharmaceuticals currently used in the treatment of tuberculosis. Our SAR study indicated the importance of the hydrogen bond acceptor subunit (**3a–l**), the position in the aromatic ring, the planarity of triazole and phenyl rings in these compounds, and a correlation between the uniform HOMO coefficient distribution and the anti-tubercular activity. The significant activity of **3a** and **3k** pointed them as promising lead molecules for further synthetic and biological exploration.

1. Introduction

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* and remains as a leading cause of mortality worldwide. Currently, among the infected individuals approximately eight million develop active TB, and almost two million die from this disease. Of the new TB cases reported, 95% occur in developing countries every year. World Health Organization estimates that about one-third of the world's population harbors latent infection of TB and thus declared it as a global emergency.[1–3]

The mortality and spread of this disease has been further aggravated by its synergy with Human Immunodeficiency Virus (HIV).[4,5] By destroying the two most important cells to the containment of tubercle bacilli (macrophages and CD4-receptor-bearing lymphocytes), HIV vigorously promotes the progression of recent or remotely acquired TB infection to active disease.[6] The deadly synergy between TB and HIV has led to a quadrupling of TB cases in several African and Asian countries. In fact it is estimated that eleven million adults are now co-infected with HIV and tuberculosis worldwide.[3] Thus both the current HIV pandemic

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and multidrug-resistant *M. tuberculosis* have emerged as major obstacles for treatment and public health control of tuberculosis.[1,2]

Chemotherapy of TB started in the 1940s and since then some agents have been discovered, including *p*-aminosalicylic acid (PAS), isoniazide (INH), pyrazinamide (PZA), cycloserine, ethionamide, rifampicin, and ethambutol.[7] However, the emergence of multiple drug-resistant (MDR) TB revealed the urgent need for new antitubercular drugs.[8]

Internationally efforts are now being made to develop new anti-tubercular agents.[3] Several studies have indicated the potential of analogues of isoniazide[9,10] and heterocyclic compounds, such as BM212,[11,12] as tuberculostatic agents. In pursuit of this goal, our research efforts herein have been directed toward the discovery of new chemical entities that are effective as anti-tuberculosis agents.

1,2,3-Triazoles are an important class of heterocyclic compounds due to their wide range of applications including as pharmaceutical agents.[13] Literature described triazoles as antiplatelet agents,[14] dopamine D2 receptor ligands related to schizophrenia,[15] anti-inflammatory agents,[16,17] anticonvulsants,[18] β-lactamase inhibitors,[19] and antiviral[20] and antimicrobial agents.[21–23] In this paper, we describe the synthesis, the in vitro antimycobacterial profile, and the structure–activity relationship (SAR) study of new N-substituted-phenyl-1,2,3-triazole-4-carbaldehydes (**3a**–**l**). Since the introduction of fluorine atom(s) may strongly modify the physical, chemical, and biological properties in a molecule and thus may increase its biological activity, in this work we also investigated the influence of the difluoromethylene group on the antimycobacterial profile of these compounds by synthesizing N-substituted-phenyl-4-difluoromethyl-1,2,3-triazoles (**4a**–**l**).[24,25]

2. Chemistry

Different methods for synthesizing 1,2,3-triazole are described in the literature.[26] In this work, the cycloaddition reactions between diazomalonaldehyde (**1**) and aniline hydrochlorides in water (**2a**–**l**) were effectively used to prepare the N-substituted-phenyl-1,2,3-triazole-4-carbaldehydes (**3a**–**l**) in moderate-to-good yields.[27–29] Then the carbaldehyde moieties in **3a**–**l** were readily converted into difluoromethyl groups for generating **4a**–**l**, on treatment with *N*,*N*-diethylaminosulfur trifluoride (DAST).[30]

3. Pharmacology

In vitro antimycobacterial activities of compounds **3a**–**l** and **4a**–**l** were assessed against *M. tuberculosis H37Rv* strain (ATCC 27294), susceptible to both rifampin and isoniazide, and were carried out using the Microplate Alamar Blue assay (MABA), which shows good correla-

Table 1. Comparison of in vitro antimycobacterial activity of compounds **3a**–**l** and **4a**–**l** against drug-sensitive *Mycobacterium tuberculosis* H37Rv strain and molecular weight (M_W), molecular volume (M_V), c log *P* and polar surface area (PSA), and molecular electronic properties (E_{HOMO}, E_{LUMO}, dipole moment)

Compound	R	MIC (μg/mL)	Inhibition (%)	M_W	c log *P*	PSA (Å^2)	M_V (Å^3)	Dipole (debye)	E_{HOMO} (eV)	E_{LUMO} (eV)
3a	3,5-DiCl	2.5	100	242.06	3.08	100.97	224.63	2.76	−7.22	−2.33
3b	3-CN	20.0	ND[a]	198.18	1.20	170.26	215.40	3.81	−7.34	−2.39
3c	4-CN	5.0	ND	198.18	1.20	168.85	215.43	0.58	−7.31	−2.61
3d	2-OCH_3	40.0	94	203.20	1.62	105.59	221.88	6.31	−6.44	−1.69
3e	4-OCH_3	10.0	100	203.20	1.62	122.41	224.52	5.71	−6.24	−1.84
3f	2,5-$(OCH_3)_2$	80.0	59	233.22	1.57	ND[a]	251.64	5.32	−5.94	−1.69
3g	3,4-$(OCH_3)_2$	80.0	0	233.22	1.23	123.01	253.53	6.99	−6.09	−1.75
3h	3-Cl	10.0	100	207.62	2.36	103.72	209.65	3.76	−6.99	−2.17
3i	4-Cl	5.0	ND	207.62	2.36	103.72	209.70	3.04	−6.81	−2.15
3j	4-Br	5.0	100	252.07	2.51	103.72	214.49	2.92	−6.81	−2.18
3k	4-CH_3	2.5	100	187.20	2.12	103.72	214.45	5.28	−6.60	−1.92
3l	4-NO_2	20.0	ND	218.04	1.47	ND[a]	220.64	0.83	−7.45	−2.93
4a	3,5-DiCl	80.0	55	264.06	3.54	47.91	233.83	2.45	−7.17	−1.95
4b	3-CN	80.0	ND	220.18	1.72	114.45	224.58	2.95	−7.33	−2.11
4c	4-CN	20.0	ND	220.18	1.72	113.04	224.62	1.48	−7.25	−2.37
4d	2-OCH_3	40.0	86	225.19	2.11	49.78	231.08	5.95	−6.37	−1.28
4e	4-OCH_3	10.0	93	225.19	2.11	66.60	233.71	5.01	−6.17	−1.28
4f	2,5-$(OCH_3)_2$	80.0	74	255.22	2.13	ND[a]	218.84	4.83	−5.87	−1.29
4g	3,4-$(OCH_3)_2$	80.0	66	255.22	1.79	67.21	262.62	3.11	−6.93	−1.74
4h	3-Cl	80.0	54	229.61	2.77	47.91	218.84	5.13	−6.50	−1.30
4i	4-Cl	40.0	ND	229.61	2.77	47.91	218.88	2.68	−6.74	−1.72
4j	4-Br	20.0	75	274.06	2.92	47.91	223.68	2.57	−6.74	−1.76
4k	4-CH_3	40.0	87	209.19	2.38	47.91	223.64	4.80	−6.53	−1.40
4l	4-NO_2	40.0	ND	240.17	1.99	ND[a]	229.82	1.68	−7.49	−2.81
Rifampicin	—	1.0	ND	—	—	—	—	—	—	—
Ethambutol	—	3.25	ND	—	—	—	—	—	—	—

[a] ND, not determined.

tion and proportionality with BACTEC radiometric methods.[31–33] This colorimetric method uses the Alamar Blue–resazurin-based oxidation–reduction indicator to obtain drug susceptibility measurements for bacteria. The minimum inhibitory concentration (MIC, μg/mL) was defined as the lowest drug concentration that prevented a color change from blue (no growth) to pink (growth). Rifampicin and Ethambutol were used as positive controls (Table 1).

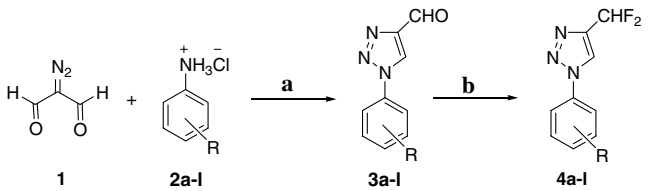
4. Results and discussion

The preparation of diazomalonaldehyde (**1**) was performed by the procedure described by Stojanovic and Arnold.[28] The reaction of **1** with appropriate aniline hydrochlorides (**2a–l**), in aqueous solution, yielded N-substituted-phenyl-1,2,3-triazole-4-carbaldehydes (**3a–l**). The new series of N-substituted-phenyl-4-difluoromethyl-1,2,3-triazoles (**4a–l**) were obtained in 90-98% yields on reaction of **3** with *N*,*N*-diethylaminosulfur trifluoride (DAST)[30] (Scheme 1).

Characterizations of **3a–l** and **4a–l** were generally carried out using microanalysis, EI-MS, IR, ^{1}H NMR, ^{13}C NMR spectroscopy, X-ray diffraction[34] and for **4a–l**, also by ^{19}F NMR spectroscopy. The ^{1}H NMR spectrums of **3a–l** showed carbaldehyde (CHO) proton as singlet at δ 10.21–10.24 ppm. Further the absence of this singlet and presence of triplet at δ 6.95–6.97 (J_{HF} = 55.5 Hz) on the ^{1}H NMR spectrums of **4a–l** indicated conversion from carbaldehyde to difluoromethyl (CHF_2).

In addition, the crystal structure of 1-(4-methylphenyl)-1,2,3-triazole-4-carbaldehyde, **3k**, grown from water, was determined by X-ray diffraction. The atom arrangements for **3k** are shown in Figure 1, where selected geometric parameters were also included. The **3k** crystal revealed that the two rings are nearly co-planar, with an angle between the two planar rings of about 7.11(12)° (Fig. 1).

All 24 compounds were active against *M. tuberculosis* although **3a–l** derivatives were significantly more effective than **4a–l** series (Table 1). This result indicated that the fluorine atom mostly negatively affected the antitubercular activity of these compounds. Interestingly 1-(3,5-dichlorophenyl)- and 1-(4-methylphenyl)-1,2,3-triazole-4-carbaldehyde, **3a** and **3k**, respectively, showed the highest activity with 100% inhibition and MIC of 2.5 μg/mL, comparable to the positive controls (Table 1). In addition compounds **3c** (R = 4-CN), **3i** (R = 4-Cl), and **3j** (R = 4-Br) also presented a potential activity (MIC = 5.0 μg/mL) as they presented MIC values lower than 6.25 μg/mL, which is currently the limiting value for evaluation of new anti-tuberculosis candidates according to the Global Discovery Program for Novel Anti-tuberculosis Drugs. The other compounds of this series and the 4-difluoromethyl derivatives displayed a lower in vitro activity against *M. tuberculosis* (MIC > 6.5 μg/mL). The most effective analogue in 4-difluoromethyl series was **4e** (R = 4-OCH_3) with 93% inhibition at 10.0 μg/mL (Table 1).



Scheme 1. Synthesis of 1,2,3-triazole derivatives **3a–l** and **4a–l**. Reagents and conditions: (a) H_2O, rt, 24 h, 60–80%; (b) DAST, DCM, rt, 24 h, 90–98%. [(**a**) R = 3,5-diCl; (**b**) R = 3-CN; (**c**) R = 4-CN; (**d**) R = 2-OCH_3; (**e**) R = 4-OCH_3; (**f**) R = 2,5-(OCH_3); (**g**) R = 3,4-(OCH_3); (**h**) R = 3-Cl; (**i**) R = 4-Cl; (**j**) R = 4-Br; (**k**) R = 4-CH_3; (**l**) R = 4-NO_2].

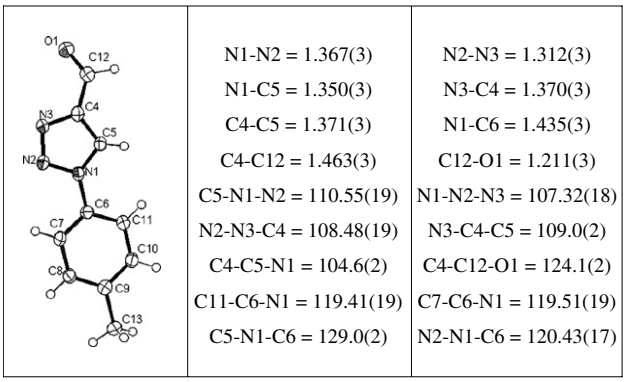


Figure 1. Molecular structure and selected geometric parameters, (Å,°), for 1-(4-methylphenyl)-1,2,3-triazole-4-carbaldehyde (**3k**).

In the effort to study the structure–activity relationships (SAR) of these compounds, we initially evaluated their hydrophobic pattern, by calculating c log *P*, molecular weight (M_W) and volume (M_V), polar surface area (PSA) (Table 1), and number of hydrogen bond acceptors and donors (not shown).[35,36] Our results pointed all compounds as sufficiently hydrophobic for penetrating the biological membranes, probably including the cellular wall of the mycobacterium, as determined by Lipinski rule of 5 (c log *P* < 5, molecular weight (M_W) ⩽500, and PSA ⩽140 Å^2, number of hydrogen bond acceptors <10 and donors <5).[35] The only exceptions were **3b** and **3c** with PSA of 170.26 and 168.85 Å^2 (Table 1). Importantly the analysis of hydrogen donors and acceptors showed that **3a–l** and **4a–l** series differed from the number of hydrogen bond acceptors (carbaldehyde replaced at R_1) (not shown). Since **3a–l** derivatives were more active than 4-difluoromethyl derivatives (**4a–l**), the carbaldehyde group seems to be important to the interaction with the target receptor and consequently influences the inhibitory profile of these compounds (Fig. 2 and Table 1).

In the conformational analysis of all compounds using molecular mechanics methods, the structures were minimized and equilibrium geometry was obtained using semi-empirical AM1 method. They were submitted to a Single Point calculation on the base of DFT methods at B3lYP/6-31G* level.[37] Then structural and electronic properties of the compounds such as

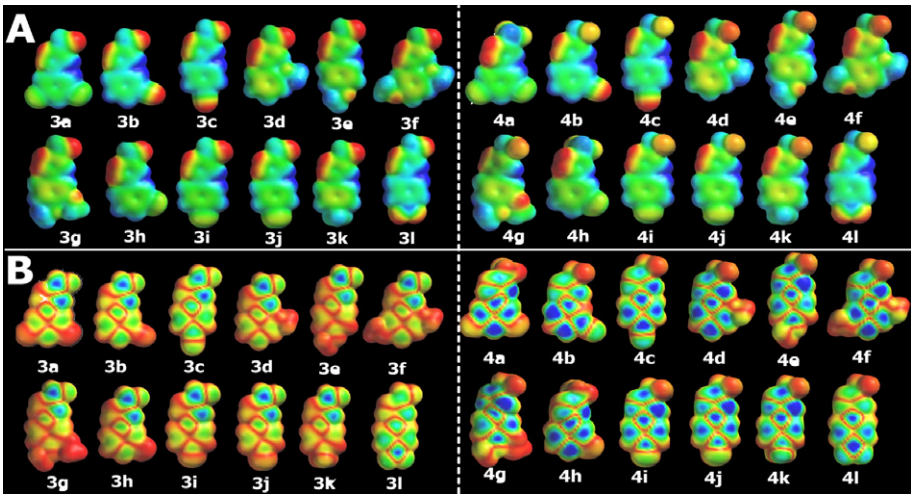


Figure 2. Comparison of molecular electrostatic potential energy isosurfaces (MEP) and LUMO density of carbaldehydes (**3a**–**l**) and fluoride derivatives (**4a**–**l**) (A) MEP superimposed onto total electron density of 0.002 e/au^3. The color code is in the range of −65.0 (deepest red) to −23.0 (deepest blue) kcal/mol. (B) LUMO density encoded onto a van der Waals surface (isodensity 0.002 e/au^3) with the LUMO's absolute density coefficient mapped from deepest red (0.00) to deepest blue (0.03).

HOMO and LUMO (energy, coefficient orbital and density), and dipole moment were calculated to gain insight about their role in modulating the antimicrobial activity studied. The overall analysis of HOMO and LUMO energy values of the **3a**–**l** and **4a**–**l** series revealed that both widely varied (HOMO −5.94 to −7.45 eV and −5.87 to −7.49 eV, and LUMO −1.69 to −2.93 eV and −1.28 to −2.81 eV, respectively) but without any clear or direct correlation with the antimycobacterial activity (Table 1). Similarly, the dipole moment did not show any further clue about the biological activity profile of these series, excluding this feature as crucial for displaying the studied activity.

In this work, the electron density/LUMO was taken into consideration where the blue and red areas around atoms indicate a large and a small LUMO values, respectively. Our results showed that **4a**–**l** derivatives have the most intense blue, which represents the largest high orbital density, compared to **3a**–**l** series. The LUMO density of **3a**–**l** series is concentrated over phenyl ring compared to the 4-difluoromethyl derivatives (**4a**–**l**), in which it is distributed along the structure (Fig. 2). This result pointed the LUMO electronic density mainly on the topside of the **3a**–**l** derivatives structure is important for displaying a significant antimycobacterial activity.

The molecular electrostatic potential map (MEP) is an alternative approach for understanding the electrostatic contribution to binding between receptor and drugs. The SAR studies involving the MEP of these derivatives pointed that the introduction of fluorine atom(s) modified the molecular electrostatic distribution in **4a**–**l**, which presented a lower biological profile (Fig. 2 and Table 1). Therefore, the loss of this negative region on the top of the molecule by the addition of the fluorine seemed to be deleterious to the anti-tubercular activity of these compounds.

The individual analysis of the compounds of the more active series with carbaldehyde at R_1 (**3a**–**l**) revealed the dipole moment vector directed from phenyl ring to the triazole moiety, except for **3c** and **3l**, which presented electron-withdrawing groups in *para*-position (not shown). The addition of a methyl substituent, a weak electron-donating group, at *para*-position of aromatic ring (**3k**) led to a slight negative potential (red region) on the ring and a high inhibitory activity as can be observed in the three-dimensional MEP (Fig. 2). The compound also showed distribution of HOMO through both rings, although most of them concentrate in the aromatic ring, which may have pointed it as the most likely region for stacking interactions with the target (Fig. 3A). In fact the overall analysis of HOMO orbital coefficient distribution of **3a**–**l** in comparison to MIC values revealed the importance of its uniform distribution along the molecule instead of its concentration on one part of it for the biological activity evaluated (Fig. 3).

The evaluation of the stereoelectronic effects when the oxygen is present in the *para* substituent (**3e**) revealed that although a methoxy analogue may allow the participation of the free electron pairs on the oxygen by resonance and the increase of the electron density in the aromatic system, the compound **3e** exhibited a 4-fold decrease in activity (Table 1). The addition of an extra methoxy group at *meta*-positions led to an even less active compound (**3g**) revealing the importance of the volume in this context (Fig. 2). Adding methoxy at *ortho*-position (**3d**) there was a 16-fold loss of activity and a 28°-torsion of the aromatic ring out of the plane also called as *ortho*-effect in the literature, which currently affects the biological activity of the compound, herein seen as a deleterious effect. Importantly, there was a significant loss of activity when an extra methoxy group (**3f**) was added (Table 1). The **3f** and **3g** results suggested that a high molecular volume (MV) may compromise the interaction with

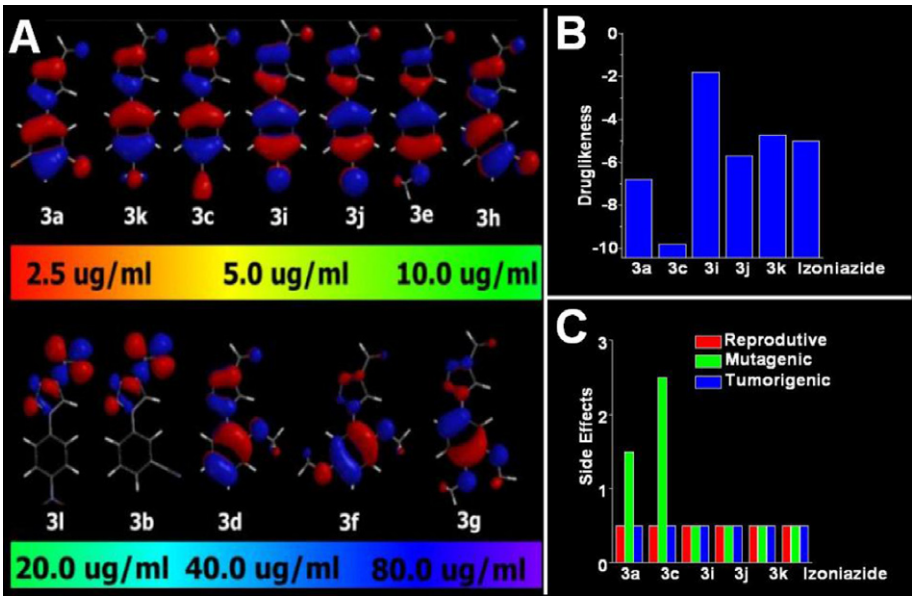


Figure 3. Comparison of HOMO coefficient distribution and MIC of **3a**–**l** derivatives (A), and druglikeness value (B) and theoretical toxicity risks of presenting mutagenic, tumorigenic, and reproductive effects (C) of the most active compounds and isoniazide using Osiris program (http://www.organic-chemistry.org/prog/peo/druglikeness.html). The scale of side effects ranges from low (0–1) to high (2–3) toxicity profile.

the target (Table 1). In addition, the presence of stereoelectronic effects depending on the position of the aromatic ring could also affect the biological activity (Fig. 2 and Table 1).

Replacement of a nitrile at *para*-position (**3c**) led to significant changes in MV and an increase of the inhibitory potential compared to the methoxy analogues (Table 1). The transposition of the substituent to a *meta*-position (**3b**) led to an 8-fold drop in activity and dislocation of HOMO to the carbaldehyde moiety (Fig. 3). This result reinforced the importance of the *para*-position in the ring for the biological activity.

Substitution of NO_2 at *para*-position (**3l**) decreased four times the inhibitory potential of the compound, compared to its analogues (**3c**). Since NO_2 is a high electron-withdrawing group, the dislocation of HOMO to the carbaldehyde moiety was observed (Fig. 3A). Setting a weak electron-withdrawing group, as Cl (**3i**) or Br (**3j**), at *para*-position increased the lipophilicity but decreased the activity 4-fold compared to the most active (Table 1). The addition of chlorine at *meta*-position of compound **3h** decreased the activity two times, which pointed the position as important as the electronic and lipophilic features. Interestingly, the addition of an extra chlorine substituent at position 5 (**3a**) led to the highest inhibitory activity, and a similar MEP, HOMO orbital coefficient and LUMO density compared to compound (**3k**) (Fig. 2 and Table 1). Apparently there is a clear correlation between the HOMO coefficient distribution and the biological profile of these molecules (Fig. 3A). This correlation is characterized by a broad HOMO distribution through the molecule structure for displaying significant antimicrobial profile while the location of this coefficient in one side of the molecule may lead to weak compounds (Fig. 3A).

Currently, there are many approaches that assess druglikeness to compounds based on topological descriptors, fingerprints of molecular druglikeness, structural keys or other properties as clog*P* and molecular weights.[38] In case of Osiris program, the occurrence frequency of each fragment is determined within the collection of traded drugs and within the supposedly non-druglike collection of Fluka compounds. On that case a value between −5 and 5 indicates that the molecule contains predominantly fragments, which are frequently present in commercial drugs. In this work we used the Osiris program for calculating the fragment-based druglikeness of the most active compounds (**3a**, **3c**, **3i**, **3j**, and **3k**) also using isoniazide, a tuberculostatic drug, as positive control for the calculation due to its structural closeness with our derivatives. Interestingly, only **3c** (MIC = 5.0 μg/ml) presented a non-potential druglikeness while **3i** presented the best value among them including isoniazide (Fig. 3B). In agreement, **3c** presented the worst prediction of one of the toxicity risks (mutagenic, tumorigenic, and reproductive effects) calculated for these most active compounds using the Osiris Property Explorer (http://www.organic-chemistry.org/). The predicted mutagenic profile of **3c** is a direct indication of its non-potential druglikeness. The low theoretical mutagenic, tumorigenic, and reproductive effects of the other compounds (**3i**, **3j**, and **3k**) indicated a low risk drug-like profile; similar to isoniazide that in the analyzed aspects was also safe. It is important to notice that the toxicity predicted herein neither is a fully reliable toxicity prediction, nor guarantees that these compounds are completely free of any toxic effect. However it reinforced the promising profile of these compounds for further experimental investigation.

5. Conclusion

To summarize, herein we described two series of 1,2,3-triazoles compounds with antimycobacterial profile. The in vitro anti-tuberculosis screening of these series showed that all compounds were active, although in general the triazole-4-carbaldehyde derivatives (**3a**–**l**) were more effective than the 4-difluoromethyl derivatives (**4a**–**l**). Our SAR study indicated the importance of the hydrogen bond acceptor subunit (**3a**–**l**), the position in the aromatic ring, the planarity of triazole and phenyl rings and the uniform HOMO coefficient distribution in these compounds for the anti-tubercular activity. Although the Osiris risk alerts are not a fully reliable toxicity prediction, the theoretical low-toxicity profile of these compounds reinforces the significant activity of **3i**, **3j**, and **3k** and pointed them as promising lead molecules for further synthetic and biological exploration.

6. Experimental protocol

6.1. Chemistry

Melting points were determined with a Buchi Model B-545 instrument and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer model 1420 FT-IR Spectrophotometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance 500 plus 400.00 and 500.00 MHz, employing tetramethylsilane as the internal reference at room temperature. ^{19}F NMR spectra were recorded on Brucker UltraShield plus 376.0 MHz, employing $CFCl_3$ as internal reference at room temperature. The chemical shifts (δ) are reported in parts per million and the coupling constant (J) in hertz. Mass spectra were recorded on CGMS (Hewlett Packard Model AT-6890N) autosampler/direct injection (EI/CI). Reactions were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F_{254} Merck plates. Microanalyses were performed on Perkin-Elmer Model 2400 instrument and all values were within ±0.4% of the calculated compositions. Chemicals employed were obtained from commercial supplies and used without purifications, unless otherwise stated.

6.1.1. General procedures

6.1.1.1. General procedure for the preparation of N-substituted-phenyl-1,2,3-triazole-4-carbaldehydes (3a–l). A solution of diazomalonaldehyde (**1**) (5.0 mmol) in water (30 mL) was added dropwise to a stirred solution of an aniline hydrochloride (**2a**–**l**) (4.5 mmol) in water (5 mL). The reaction mixture was stirred for 24 h at room temperature, the solid was collected, washed with cold water, and recrystallized from ethanol/water. The following compounds were prepared according to this general procedure.

6.1.1.2. 1-(3,5-Dichlorophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3a). Obtained in 73% yield as white solid; mp 156–158 °C; IR (KBr) ν_{max} (cm^{-1}) 3126, 3085, 1690 (C=O); ^{1}H NMR (500 MHz; $CDCl_3$/Me_4Si): δ 7.52 (d, 1H, J = 1.5 Hz, arom.); 7.75 (d, 2H, J = 1.5 Hz; arom.); 8.75 (s, 1H, triazole); 10.22 (s, 1H, HC=O); ^{13}C NMR (125 MHz; $CDCl_3$/Me_4Si): δ 119.3, 123.0, 129.8, 136.6, 137.3, 148.3, 184.6 (HC=O); EIMS (*m*/*z*): 241 (M^+; 18%); 212 (M^+-29; 100%); Anal. Calcd for $C_9H_5Cl_2N_3O$: C, 44.66; H, 2.07; N, 17.36. Found: C, 44.66; H, 2.07; N, 17.36.

6.1.1.3. 1-(3-Cyanophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3b). Obtained in 80% yield as white solid crystals; mp 177–179 °C; IR (KBr) ν_{max} (cm^{-1}) 3130, 2839, 2234 (CN), 1697 (C=O); ^{1}H NMR (500 MHz; $CDCl_3$/Me_4Si): δ 7.75 (t, 1H, J = 8.0 Hz, 0.5 Hz; arom.); 8.06 (ddd, 1H, J = 1.2, 8.0 Hz; arom.); 7.84 (dt, 1H, J = 1.0, 8.0 Hz; arom.); 8.15 (t, 1H, J = 2.0 Hz; arom.); 8.61 (s, 1H, triazole); 10.24 (s, 1H, HC=O); ^{13}C NMR (125 MHz; $CDCl_3$/Me_4Si): δ 114.6, 117.0 (CN), 124.7, 133.1, 124.1, 131.2, 122.9, 136.7, 148.0, 184.6 (HC=O); EIMS (*m*/*z*): 198 (M^+, 9%); 169 (M^+-29; 100%); Anal. Calcd for $C_{10}H_6N_4O$: C, 60.60; H, 3.05; N, 28.27. Found: C, 60.60; H, 3.05; N, 28.27.

6.1.1.4. 1-(4-Cyanophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3c). Obtained in 75% yield as white solid crystals; mp 178–179 °C; IR (KBr) ν_{max} (cm^{-1}) 3116, 2865, 2232 (CN), 1697 (C=O); ^{1}H NMR (500 MHz; DMSO-d_6/Me_4Si): δ 8.14 (d, 2H, J = 9.0 Hz; arom.); 8.24 (d, 2H, J = 9.0 Hz; arom.); 9.71 (s, 1H, triazole); 10.14 (s, 1H, HC=O); ^{13}C NMR (125 MHz; DMSO-d_6/Me_4Si): δ 111.8, 117.8 (CN), 126.4, 121.1, 134.2, 138.8, 147.6, 184.6 (HC=O); EIMS (*m*/*z*): 198 (M^+, 10%); 169 (M^+-29; 100%); Anal. Calcd for $C_{10}H_6N_4O$: C, 60.60; H, 3.05; N, 28.27. Found: C, 60.60; H, 3.05; N, 28.27.

6.1.1.5. 1-(2-Methoxyphenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3d). Obtained in 66% yield as yellow solid; mp 108–109 °C; IR (KBr) ν_{max} (cm^{-1}) 3157, 2979, 1685 (C=O); ^{1}H NMR (500 MHz; $CDCl_3$/Me_4Si): δ 3.93 (s, OCH_3); 7.15 (m, 2H, arom.); 7.47 (ddd, 1H, J = 1.5, 8.0 Hz; arom.); 7.87 (dd,1H, J = 1.5, 6.5, 8.0 Hz; arom.); 8.72 (s, 1H, triazole); 10.24 (s, 1H, HC=O); ^{13}C NMR (125 MHz; $CDCl_3$/Me_4Si): 56.0 (OCH_3); 112.3, 125.2, 121.3, 130.9, 127.3, 147.3, 150.8, 185.3 (HC=O); EIMS (*m*/*z*): 203 (M^+; 38%); 174 (M^+-29; 30%); 77 (M^+-126; 100%); Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.43; N, 20.69. Found: C, 59.11; H, 4.43; N, 20.68.

6.1.1.6. 1-(4-Methoxyphenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3e). Obtained in 76% yield as white solid; mp 158–161 °C; IR (KBr) ν_{max} (cm^{-1}) 3157, 2979, 1685 (C=O); ^{1}H NMR (500 MHz; $CDCl_3$/Me_4Si): δ 3.89 (s, OCH_3); 7.06 (ddd, 2H, J = 4.5, 9.0 Hz, arom.); 7.66 (ddd, 2H, J = 4.5, 9.0 Hz, arom.); 8.46 (s, 1H, triazole); 10.21 (s, 1H, HC=O); ^{13}C NMR (125 MHz; $CDCl_3$/Me_4Si): 55.7 (OCH_3), 123.0; 129.4, 122.4, 115.0, 148.5, 160.5, 185.1 (HC=O); EIMS (*m*/*z*): 203 (M^+; 39%); 174 (M^+-29; 40%); 132 (M^+-71; 100%); Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.43; N, 20.69. Found: C, 59.11; H, 4.43; N, 20.69.

6.1.1.7. 1-(2,5-Dimethoxyphenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3f). Obtained in 73% yield as yellow solid; mp 89 °C; IR (KBr) ν_{max} (cm^{-1}) 3369, 2929, 1697 (C=O); ^{1}H NMR (500 MHz; $CDCl_3$/Me_4Si): δ 3.85 (s, OCH_3); 3.88 (s, OCH_3); 7.01 (dd, 1H, J = 3.0, 9.0 Hz;

arom.); 7.06 (d, 1H, J = 9.0 Hz); 7.49 (d, 1H, J = 3.0, 9.0 Hz; arom.); 8.79 (s, 1H, triazole); 10.23 (s, 1H, HC=O); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 55.7 (OCH_3), 123.0, 129.4, 122.4, 115.0, 148.5, 160.5, 185.1 (HC=O); EIMS (*m*/*z*): 233 (M^+; 45%); 204 (M^+-29; 40%); 162 (M^+-71; 100%); Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.64; H, 4.77; N, 18.02.

6.1.1.8. 1-(3,4-Dimethoxyphenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3g). Obtained in 80% yield as yellow solid; mp 170–171 °C; IR (KBr) ν_{max} (cm^{-1}) 3131, 2970, 1693 (C=O); ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 3.96 (s, OCH_3); 3.98 (s, OCH_3); 6.99 (d,1H, J = 8.5 Hz, arom.); 7.23 (dd, 1H, J = 2.5, 8.5 Hz, arom.); 7.36 (d, 1H, J = 2.5 Hz, arom.); 8.49 (s, 1H, triazole); 10.21 (s, 1H, HC=O); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 56.2 (OCH_3); 56.3 (OCH_3); 105.0, 111.2, 112.8, 129.5, 123.1, 148.0, 149.9, 150.1, 185.1 (HC=O); EIMS (*m*/*z*): 233 (M^+; 50%); 204 (M^+-29; 9%); 162 (M^+-71; 100%); Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.65; H, 4.75; N, 18.02.

6.1.1.9. 1-(3-Chlorophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3h). Obtained in 73% yield as yellow solid; mp 129–130 °C; IR (KBr) ν_{max} (cm^{-1}) 3127, 2874, 1701 (C=O); ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 7.51 (m, 2H, arom.); 7.85 (t, 1H, J = 1.5, 3.0 Hz, arom.); 7.68 (ddd, 1H, J = 1.5, 3.0, 8.0 Hz, arom.); 8.55 (s, 1H, triazole); 10.23 (s, 1H, HC=O); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 118.8, 121.2, 123.0, 129.5, 131.1, 135.9, 136.9, 148.2, 184.8 (HC=O); EIMS (*m*/*z*): 207 (M^+; 18%); 178 (M^+-29; 92%); 111 (M^+-96; 100%); Anal. Calcd for $C_9H_6ClN_3O$: C, 52.05; H, 2.91; N, 20.24. Found: C, 52.05; H, 2.92; N, 20.24.

6.1.1.10. 1-(4-Chlorophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3i). Obtained in 75% yield as white solid; mp 159–161 °C (lit.[14] 155–156 °C); IR (KBr) ν_{max} (cm^{-1}) 3127; 2874; 1701 (C=O); ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 7.56 (2H, d, J = 1.5, 3.0 Hz; arom.); 7.74 (2H, d, J = 7.0 Hz; arom.); 8.53 (1H, s, triazole); 10.22 (1H, s, HC=O); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 22.0, 123.0, 130.2, 134.6, 135.8, 148.2, 184.9 (HC=O); EIMS (*m*/*z*): 207 (M^+; 32%); 178 (M^+-29; 100%); Anal. Calcd for $C_9H_6ClN_3O$: C, 52.05; H, 2.91; N, 20.24. Found: C, 52.06; H, 2.91; N, 20.25.

6.1.1.11. 1-(4-Bromophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3j). Obtained in 76% yield as white solid; mp 190–191 °C; IR (KBr) ν_{max} (cm^{-1}) 3098; 2851; 1698 (C=O); ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 7.68 (d, 2H, J = 9.0 Hz, arom.); 7.72 (d, 2H, J = 9.0 Hz, arom.); 8.54 (s, 1H, triazole); 10.22 (s, 1H, HC=O); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 122.2, 122.9, 123.7, 133.2, 135.1, 148.2, 184.9 (HC=O); EIMS (*m*/*z*): 253 (M^+; 11%); 224 (M^+-29; 32%); 116 (M^+-137; 100%); Anal. Calcd for $C_9H_6BrN_3O$: C, 42.88; H, 2.40; N, 16.67. Found: C, 42.87; H, 2.41; N, 16.67.

6.1.1.12. 1-(4-Methylphenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3k). Obtained in 86% yield as white solid; mp 105–106 °C; IR (KBr) ν_{max} (cm^{-1}) 3136, 2842, 1696 (C=O); ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 2.45 (s, 1H, CH_3); 7.36 (d, 2H, J = 8.0 Hz, arom.); 7.64 (d, 2H, J = 8.0 Hz, arom.); 8.49 (s, 1H, triazole); 10.22 (s, 1H, HC=O); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 21.1 (CH_3), 140.1, 133.8, 130.5, 123.0, 120.7, 148.0, 185.1 (HC=O); EIMS (*m*/*z*): 187 (M^+; 20%); 158 (M^+-29; 52%); 130 (M^+-57; 100%); Anal. Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.16; H, 4.85; N, 22.44.

6.1.1.13. 1-(4-Nitrophenyl)-1*H*-1,2,3-triazole-4-carbaldehyde (3l). Obtained in 80% yield as yellow solid; mp185–186 °C; IR (KBr) ν_{max} (cm^{-1}) 3136; 1696 (C=O); 1524 (NO_2); ^{1}H NMR (500 MHz; DMSO-d_6/Me_4Si): δ 8.31 (d, 2H, J = 8.8 Hz); 8.48 (d, 2H, J = 8.8 Hz; arom.); 9.78 (s, 1H, triazole); 10.15 (s, 1H, HC=O); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 121.4, 125.4, 126.7, 140.2, 147.2, 147.7, 184.8 (HC=O); EIMS (*m*/*z*): 218 (M^+; 9%); 189 (M^+-29; 100%); Anal. Calcd for $C_9H_6N_4O_3$: C, 49.55; H, 2.77; N, 25.60. Found: C, 49.56; H, 2.77; N, 25.58.

6.1.1.14. General procedure for the preparation of N-substituted-phenyl-4-difluoromethyl-1,2,3-triazoles (4a–l). A solution of a N-substituted-phenyl-1,2,3-triazole-4-carbaldehyde (7.5 mmol) in dichloromethane (15 mL) was added dropwise to DAST (2 equiv) at room temperature. The reaction mixture was stirred for 24 h at room temperature, poured onto a saturated sodium bicarbonate solution at 0 °C, and extracted with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the filtrate concentrated under reduced pressure. The solid residue was purified by column chromatography using chloroform as eluent. The following compounds were prepared according to this general procedure.

6.1.1.15. 1-(3,5-Dichlorophenyl)-4-(difluoromethyl)-1*H*-1,2,3-triazole (4a). Obtained in 98% yield as white solid; mp 83–85 °C; IR (KBr) ν_{max} (cm^{-1}) 3160, 1042, ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 6.95 (t, 1H, CHF_2, J = 54.5 Hz); 7.72 (d, 1H, J = 1.5 Hz; arom.); 7.49 (dd,1H, J = 1.0, 1.5 Hz; arom.); 7.72 (d, 1H, J = 1.5 Hz; arom.); 8.24 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 109.6 (t, CHF_2, J = 235.3 Hz); 119.2, 123.0, 129.5, 136.5, 137.6, 143.9 (t, J = 29.8 Hz); ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −117.6 (2F, CHF_2); EIMS (*m*/*z*): 263 (M^+; 73%); 235 (M^+-28; 30%); 234 (M^+-29; 100%); Anal. Calcd for $C_9H_5Cl_2F_2N_3$: C, 40.94; H, 1.91; N, 15.91. Found: C, 40.94; H, 1.91; N, 15.91.

6.1.1.16. 1-(3-Cyanophenyl)-4-(difluoromethyl)-1*H*-1,2,3-triazole (4b). Obtained in 97% yield as white solid; mp 119–120 °C; IR (KBr) ν_{max} (cm^{-1}) 3156, 2235 (CN), 1042; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 6.97 (t, 1H, CHF_2, J = 54.5 Hz); 8.12 (dd, 1H, J = 1.5, 2.0 Hz; arom.); 8.06 (ddd,1H, J = 1.0, 2.0, 3.0, 8.5 Hz, arom.); 7.81 (dd, 1H, J = 1.0, 7.0 Hz, arom.); 7.74 (d, 1H, J = 8.0 Hz; arom.) 8.33 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 109.6 (t, CHF_2, J = 237.3 Hz); 114.4, 117.1 (CN); 120.0, 124.0, 124.7,

131.1, 132.8, 137.0, 143.9 (t, $J = 29.5$ Hz); ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.9 (2F, CHF_2); EIMS (*m/z*): 220 (M^+; 24%); 192 (M^+-28; 20%); 191 (M^+-29; 63%); 173 (M^+-47; 52%); 128 (M^+-92; 45%); 102 (M^+-118; 100%); Anal. Calcd for $C_{10}H_6F_2N_4$: C, 54.55; H, 2.75; N, 25.45. Found: C, 54.55; H, 2.75; N, 25.45.

6.1.1.17. 1-(4-Cyanophenyl)-4-(difluoromethyl)-1*H*-1,2,3-triazole (4c). Obtained in 98% yield as white solid; mp 126–128 °C; IR (KBr) ν_{max} (cm^{-1}) 3139, 2235 (CN), 1040; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 6.97 (t, 1H, CHF_2, $J = 54.5$ Hz); 7.89 (dd, 2H, $J = 2.0$, 7.0 Hz; arom.); 7.96 (dd, 1H, $J = 1.5$, 7.0 Hz; arom.); 8.35 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 109.7 (t, CHF_2, $J = 235.0$ Hz); 114.4, 117.1 (CN), 120.0, 124.0, 124.7, 131.1, 132.8, 137.0, 143.9 (t, $J = 29.1$ Hz); ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.9 (2F, CHF_2); EIMS (*m/z*): 220 (M^+; 42%); 192 (M^+-28; 42%); 191 (M^+-29; 100%); Anal. Calcd for $C_{10}H_6F_2N_4$: C, 54.55; H, 2.75; N, 25.45. Found: C, 54.55; H, 2.75; N, 25.45.

6.1.1.18. 4-(Difluoromethyl)-1-(2-methoxyphenyl)-1*H*-1,2,3-triazole (4d). Obtained in 96% yield as white solid; mp 65–66 °C; IR (KBr) ν_{max} (cm^{-1}) 3160, 1035; ^{1}H NMR (400 MHz; $CDCl_3/Me_4Si$): δ 3.92 (d, 1H, OCH_3, $J = 4.0$ Hz); 6.97 (t, CHF_2,$J = 72.0$ Hz); 7.12 (d, 2H, $J = 8.0$ Hz, arom.); 7.46 (ddd, 1H, $J = 4.0$; 8.0 Hz; arom.); 7.79 (d, 1H, $J = 8.0$ Hz, arom.); 8.07 (s, 1H, triazole); ^{13}C NMR (100 MHz; $CDCl_3/Me_4Si$): δ 56.0 (OCH_3); 110.3 (t, CHF_2, $J = 235.0$ Hz); 112.3, 124.4, 121.3, 125.4, 130.6, 151.0, 137.0, 142.2; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.1 (2F,CHF_2); EIMS (*m/z*): 225 (M^+; 90%); 196 (M^+-29; 18%); 191 (M^+-29; 100%); Anal. Calcd for $C_{10}H_9F_2N_3O$: C, 53.33; H, 4.03; N, 18.66. Found: C, 53.34; H, 4.04; N, 18.66.

6.1.1.19. 4-(Difluoromethy)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole (4e). Obtained in 97% yield as white solid; mp 98–100 °C; IR (KBr) ν_{max} (cm^{-1}) 3097, 1051, 1023; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 3.89 (s, OCH_3); 6.95 (t, 1H, CHF_2, $J = 55.0$ Hz); 7.04 (dd, 2H, $J = 2.0$, 7.0 Hz; arom.); 7.63 (dd, 2H, $J = 2.0$, 7.0 Hz; arom.); 8.14 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 55.6 (OCH_3); 110.1 (t, CHF_2, $J = 234.7$ Hz); 115.0, 120.6, 122.5, 160.3, 129.8, 143.2 (t, $J = 29.1$ Hz); ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.2 (2F, CHF_2); EIMS (*m/z*): 225 (M^+; 36%); 197 (M^+-28; 15%); 182 (M^+-43; 100%); Anal. Calcd for $C_{10}H_9F_2N_3O$: C, 53.33; H, 4.03; N, 18.66. Found: C, 53.33; H, 4.03; N, 18.66.

6.1.1.20. 4-(Difluoromethyl)-1-(2,5-dimethoxyphenyl)-1*H*-1,2,3-triazole (4f). Obtained in 98% yield as white solid; mp 78–79 °C; IR (KBr) ν_{max} (cm^{-1}) 3169, 1027; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 3.89 (s, OCH_3); 6.95 (t, 1H, CHF_2, $J = 55.0$ Hz); 7.04 (dd, 2H, $J = 2.0$, 7.0 Hz; arom.); 7.63 (dd, 2H, $J = 2.0$,7.0 Hz; arom.); 8.14 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 55.9 (OCH_3); 56.5 (OCH_3); 110.3 (t, CF_2H, $J = 230.0$ Hz); 113.6, 116.2, 124.4, 121.1, 127.3, 142.3 (t, $J = 29.1$ Hz) 144.7, 153.9; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.2 (2F,CHF_2); EIMS (*m/z*): 255 (M^+; 60%); 227 (M^+-28; 8%); 226 (M^+-29; 5%); 212 (M^+-43; 100%); Anal. Calcd for $C_{11}H_{11}F_2N_3O_2$: C, 51.77; H, 4.34; N, 16.46. Found: C, 51.77; H, 4.34; N, 16.46.

6.1.1.21. 4-(Difluoromethyl)-1-(3,4-dimethoxyphenyl)-1*H*-1,2,3-triazole (4g). Obtained in 95% yield as white solid; mp 62–63 °C; IR (KBr) ν_{max} (cm^{-1}) 3160, 1035; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 3.96 (s, 6H, OCH_3); 6.95 (t, 1H, CHF_2, $J = 54.3$ Hz); 6.97 (d,1H, $J = 9.0$ Hz, arom.); 7.33 (d, 1H, $J = 2.5$ Hz; arom.); 7.18 (dd, 1H, $J = 2.5$, 8.5 Hz, arom.); 8.16 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 56.2, 110.0 (t, CF_2H, $J = 234.5$ Hz); 120.7, 111.1, 112.8, 105.1, 129.9, 143.2 (t, $J = 29.0$ Hz); 149.8; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.2 (2F,CHF_2); EIMS (*m/z*): 255 (M^+; 60%); 277 (M^+-28; 8%); 226 (M^+-29; 5%); 208 (M^+-47; 6%); Anal. Calcd for $C_{11}H_{11}F_2N_3O_2$: C, 51.77; H, 4.34; N, 16,46. Found: C, 51.77; H, 4.34; N, 16.46.

6.1.1.22. 1-(3-Chlorophenyl)-4-(difluoromethyl)-1*H*-1,2,3-triazole (4h). Obtained in 93% yield as white solid; mp 57–58 °C; IR (KBr) ν_{max} (cm^{-1}) 3146, 1042; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 6.96 (t, 1H, CHF_2, $J = 54.5$ Hz); 7.8 (d, 1H, $J = 1.5$ Hz, arom.); 7.66 (dd,1H, $J = 1.2$, 7.5 Hz, arom.); 7.65 (m); 8.24 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 109.8 (t, CF_2H, $J = 236.5$ Hz); 120.5, 118.8, 121.1, 131.0, 135.4, 137.2, 143.6 (t, $J = 28.1$ Hz); 135.8; ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.6 (2F, CHF_2); EIMS (*m/z*): 229 (M^+ 60%); 200 ($M^{\cdot+}-29$; 72%); 182 ($M^{\cdot+}-47$; 60%); 137 ($M^{\cdot+}-92$; 50%); 111 ($M^{\cdot+}-118$; 100%); Anal. Calcd for $C_9H_6ClF_2N_3$: C, 47.08; H, 2.62; N, 18.30. Found: C, 47.08; H, 2.62; N, 18.29.

6.1.1.23. 1-(4-Chlorophenyl)-4-(difluoromethyl)-1*H*-1,2,3-triazole (4i). Obtained in 95% yield as white solid; mp 122–124 °C; IR (KBr) ν_{max} (cm^{-1}) 3150, 1046; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 6.95 (t, 1H, CF_2H, $J = 54.5$ Hz); 7.71 (d, 2H, $J = 7.0$ Hz, arom.); 7.54 (d, 2H, $J = 7.0$ Hz, arom.); 8.21 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 109.9 (t, CF_2H, $J = 236.5$ Hz); 120.5, 134.9, 135.4, 122.0, 130.1, 143.7 (t, C4, $J = 28.1$ Hz); ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.5 (2F, CHF_2); EIMS (*m/z*): 229 (M^+; 60%); 220 (M^+-29; 68%); 182 (M^+-47; 80%); 137 (M^+-92; 67%); 111 (M^+-118; 100%) Anal. Calcd for $C_9H_6ClF_2N_3$; C, 47.08; H, 2.63; N, 18.30. Found: C, 47.07; H, 2.64; N, 18.30.

6.1.1.24. 1-(4-Bromophenyl)-4-(difluoromethyl)-1*H*-1,2,3-triazole (4j). Obtained in 95% yield as white solid; mp 141–144 °C; IR (KBr) ν_{max} (cm^{-1}) 3152, 1043; ^{1}H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 6.94 (t, 1H, CF_2H, $J = 68.0$ Hz); 7.64 (d, 2H, $J = 11.0$ Hz, arom.); 7.69 (d, 2H, $J = 11.0$ Hz, arom.); 8,20 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 109.5 (t, CF_2H, $J = 233.2$ Hz); 120.4, 135.5, 122.2, 133.6, 133.1, 143.7 (t, $J = 28.5$ Hz). ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.5 (2F, CHF_2); EIMS (*m/z*): 273 (M^+; 85%); 245

(M^+-28; 33%); 226 (M^+-49; 60%); 181 (M^+-94; 50%); 154 (M^+-119; 83%); 166 (M^+-109; 100%); Anal. Calcd for $C_9H_6BrF_2N_3$: C, 39.44; H, 2.04; N, 15.33. Found: C, 39.45; H, 2.01; N, 15.32.

6.1.1.25. 4-(Difluoromethyl)-1-(4-methylphenyl)-1*H*-1,2,3-triazole (4k). Obtained in 93% yield as white solid; mp 96–97 °C; IR (KBr) ν_{max} (cm^{-1}) 3162, 1031, 3152, 1043; ^1H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 2.43 (s, 1H, CH_3); 6.94 (t, 1H, CF_2H, $J = 54.5$ Hz); 7.31 (d, 2H, $J = 8.8$ Hz; arom.); 7.60 (d, 2H, $J = 8.8$ Hz, arom.); 8,18 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 20.5 (CH_3); 109.5 (t, CF_2H, $J = 233.4$ Hz); 119.9, 139.1, 133.6, 129.8, 120.1, 142.7 (t, $J = 28.5$ Hz); ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −112.3 (2F, CHF_2); EIMS (*m/z*): 209 (M^+; 42%); 180 (M^+-29; 68%);162 (M^+-47; 40%); 130 (M^+-79; 42%); 91 (M^+-118; 100%); Anal. Calcd for $C_{10}H_9F_2N_3$; C, 57.41; H, 4.34; N, 20.09. Found: C, 57.41; H, 4.34; N, 20.08.

6.1.1.26. 4-(Difluoromethyl)-1-(4-nitrophenyl)-1*H*-1,2,3-triazole (4l). Obtained in 93% yield as white solid; mp 161–163 °C; IR (KBr) ν_{max} (cm^{-1}) 3142, 1526, 1341, 1039; ^1H NMR (500 MHz; $CDCl_3/Me_4Si$): δ 6.98 (t,1H, CF_2H, $J = 54.5$ Hz); 8.02 (d, 2H, $J = 7.5$ Hz, arom.); 8.47 (d, 2H, $J = 7.5$ Hz, arom.); 8.35 (s, 1H, triazole); ^{13}C NMR (125 MHz; $CDCl_3/Me_4Si$): δ 109.6 (t, CF_2H, $J = 236.9$ Hz); 120.5, 120.9, 125.6, 140.5, 144.2, 147.7. ^{19}F NMR (376.0 MHz, $CDCl_3/CFCl_3$): δ −113.0 (2F, CHF_2); EIMS (*m/z*): 240 (M^+; 30%); 212 (M^+-28; 40%); 211 (M^+-29; 32%); 193 (M^+-47; 18%); 166 (M^+-74; 28%); 76 (M^+-164, 100%); Anal. Calcd for $C_9H_6F_2N_4O_2$: C, 45.01; H, 2.53; N, 23.33. Found: C, 45.01; H, 2.53; N, 23.33.

6.2. Antimycobacterial assay

Two hundred microliters of sterile deionized water was added to all outer-perimeter wells of sterile 96-well plates (Falcon, 3072: Becton–Dickinson, Lincoln Park, NJ) to minimize evaporation of the medium in the test wells during incubation. The 96 well-plates received 100 μL of the Middlebrook 7H9 broth (Difco Laboratories, Detroit, MI, USA) and a serial dilution of the compounds **3a**–**l** and **4a**–**l** was made directly on the plate. The final drug concentrations tested were 1.0–100.0 μg/mL. The plates were sealed with Parafilm and incubated at 37 °C for five days. After this time, 25 μL of a freshly prepared 1:1 mixture of 10× Alamar Blue (Accumed International, Westlake Ohio) reagent and 10% Tween 80 was added to the plate and reincubated at 37 °C for 24 h, and the colors of all wells were recorded.

6.3. Molecular modeling and SAR studies

Molecular modeling was performed using SPARTAN'04 (Wavefunction Inc. Irvine, CA, 2000), Molecular Spreadsheet/QSAR module/SYBYL v6.8 running on SGI/Origin computer (installed at Programa de Computação Científica, FIOCRUZ) and Osiris programs (http://www.organic-chemistry.org/prog/peo/druglikeness.html). Structures were minimized and the equilibrium geometry was obtained in vacuum using a semi-empirical AM1 module. In order to evaluate the electronic properties of the AM1 minimal energy conformations, they were submitted to a single-point calculation using DFT method with a 6-31-G* basis set of the SPARTAN'04 package. The three-dimensional isosurfaces of the molecular electrostatic potential maps (MEPs) at the van der Waals contact surface represented electrostatic potentials superimposed onto a surface of constant electron density (0.002 e/au^3). They were generated in a range from −65 to +23 kcal/mol. These color-coded isosurface values provide an indication of the overall molecular size and location of negative (red) or positive (blue) electrostatic potentials. The electronic properties (HOMO's energy, HOMO orbital coefficients' distribution, LUMO density, dipole moment, dipole moment vector, and lipophilicity-c log *P*) were calculated for all compounds. Theoretical log *P* (c log *P*) and polar superficial area (PSA) were calculated at SYBYL program v.6.8.

6.4. Crystal structure analysis of 1-(4-methylphenyl)-1,2,3-triazole-4-carbaldehyde (3k)

Room temperature data were collected on a Bruker SMART area CCD diffractometer whilst low temperature data were collected on an Enraf Nonius KappaCCD diffractometer at the UK's EPSRC X-ray crystallographic service, based at the University of Southampton. The structure was solved by direct methods with SHELXS-97 and refined using SHELXL-97[39] in the triclinic spacegroup *P*-1.*Crystal data*: $C_{10}H_9N_3O$, colorless, $M = 187.20$, $T = 120$ K, monoclinic, space group *Pc*, $a = 3.8806(3)$, $b = 12.6636(12)$, $c = 9.1604(9)$ Å, $\beta = 101.292(6)°$, $V = 441.45(7)$ Å^3, $Z = 2$, $D_x = 1.408$ mg/m^3, monochromatic Mo-Kα radiation, $\lambda = 0.71073$ Å, $\mu = 0.096$ mm^{-1}. Supplementary data are available from the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, fax: +44 1223 366 033, e-mail: deposit@ccdc.ac.uk or on the web www: http://www.ccdc.cam.ac.uk on request, quoting the Deposition No. CCDC 602817.

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