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Article

On the Search for Potential Antimycobacterial Drugs: Synthesis of Naphthoquinoidal, Phenazinic and 1,2,3-Triazolic Compounds and Evaluation Against *Mycobacterium tuberculosis*

Guilherme A. M. Jardim,[a] Eduardo H. G. Cruz,[a] Wagner O. Valença,[a,d] Jarbas M. Resende,[a] Bernardo L. Rodrigues,[b] Daniela F. Ramos,[c] Ronaldo N. Oliveira,[d] Pedro E. A. Silva[c,*] and Eufrânio N. da Silva Júnior[a,*]

[a]Laboratório de Química Sintética e Heterocíclica and [b]Laboratório de Cristalografia, Instituto de Ciências Exatas, Departamento de Química, Universidade Federal de Minas Gerais, 31270-901 Belo Horizonte-MG, Brazil

[c]Laboratório de Micobacterias, Faculdade de Medicina, Universidade Federal do Rio Grande, 96200-190 Rio Grande-RS, Brazil

[d]Departamento de Ciências Moleculares, Universidade Federal Rural de Pernanbuco, 52171-900 Recife-PE, Brazil

Fifteen naphthoquinones, sixteen phenazines and fifteen aryl triazoles were synthesized and evaluated against *Mycobacterium tuberculosis*. Twenty five substances are reported here for the first time and, among all of the compounds evaluated, six presented MIC (minimal inhibitory concentration) values ≤ 6.25 μg mL^{-1}. These substances are promising antimycobacterial prototypes.

Keywords: lapachol, phenazines, *Mycobacterium tuberculosis,* antitubercular, triazoles

Introduction

Tuberculosis (TB), a disease caused mainly by *Mycobacterium tuberculosis*, is responsible for approximately 1.4 million deaths annually worldwide.[1] In the absence of an effective vaccine the best way to control dissemination of TB, is by treatment, but the length of this, typically six months, is a major problem faced by patients.[2,3]

The increasing problem of multidrug resistance (MDR) and associated treatment failure represents a threat for the control of this disease. This is driving the necessity to discover new anti-TB drugs that are effective against active or persistent infections, as well as against sensitive or resistant strains. This, in turn, would lead to a reduction of the treatment time and would therefore reduce toxic effects in comparison with current chemotherapy.[4]

Although, in recent years, a large number of molecules have been identified as potential new anti-TB drugs, only a few examples have emerged for clinical use.[5] Moreover, an attractive strategy, from economical, pharmaceutical, and clinical viewpoints, is the development of new anti-TB drugs from known molecules, especially those for which anti-TB therapeutic use has already been demonstrated to be safe and effective.[6] Clofazimine, a phenazine compound, was originally reported as a potent antituberculosis agent.[7] Phenazine-1-carboxamides have also recently been described as having potent activity against *M. tuberculosis* (Figure 1).[8] Naphthoquinoidal compounds are considered to be privileged structures with remarkable pharmacological potential.[9] Lapachol (**1**) and β-lapachone (**2**) are quinones with notable activities and are representative of a select group of bioactive substances, which, for instance, exhibit antitumor[10] and trypanocidal[11] activities, and can be used as models to obtain new drugs. Recently, our research group investigated the leishmanicidal,[12] trypanocidal,[13] and antimalarial[14] activities of a large number of substances prepared from lapachol (**1**) as part of our search for new potential drugs against neglected diseases.[15,16] Within this context, we have described the synthesis and evaluation of quinonoid, naphthoimidazole, naphthoxazole,[17] and phenazine[18] compounds from lapachol (**1**) with marked activity against *M. tuberculosis* (Figure 1).

*e-mail: pedrefurg@gmail.com; eufranio@ufmg.br
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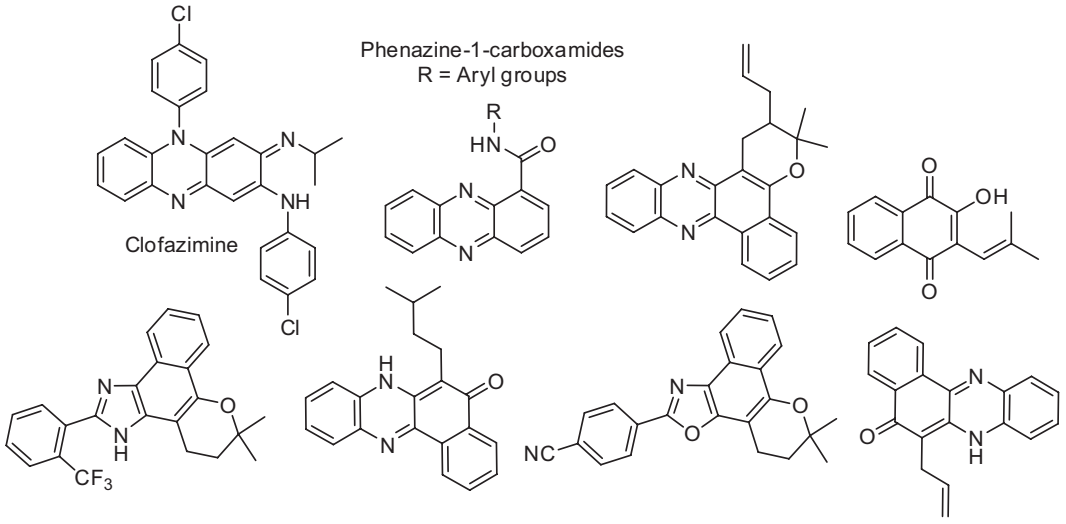


Figure 1. Clofazimine, phenazine-1-carboxamides, and examples of compounds obtained from lapachol (**1**) with activity against *M. tuberculosis*.

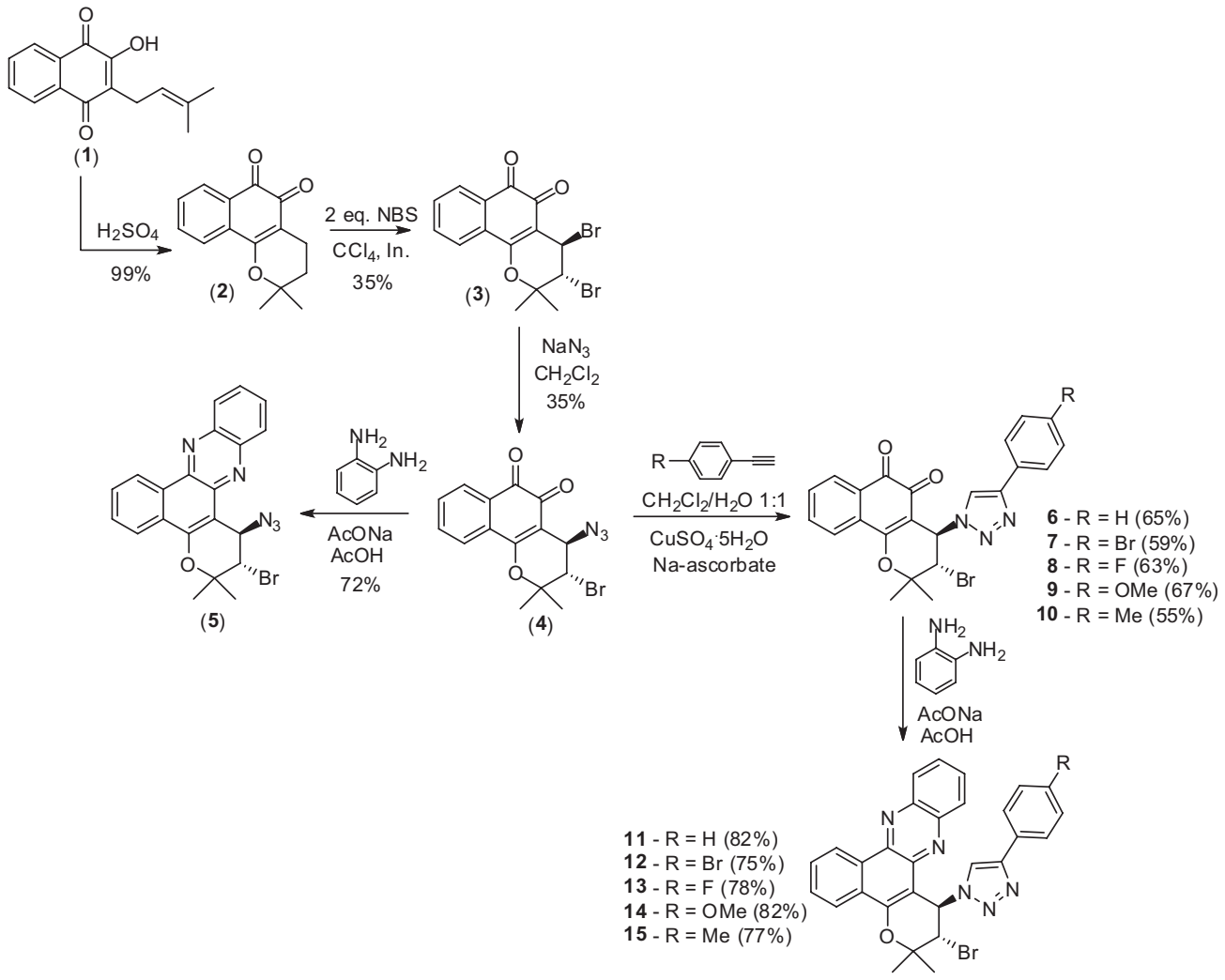
1,2,3-Triazoles are well known for their various biological activities, including anti-TB and antifungal activity, and these arise by inhibition of cell wall synthesis.[19] Recently, our group has devoted efforts to the preparation of new triazoles with potent biological activities,[15] including, for instance, β-lapachone and *nor*-β-lapachone-based 1,2,3-triazoles as potent trypanocidal compounds.[20,21] In this context, as a continuation of our programme to develop new antimycobacterial compounds, we describe herein the synthesis of lapachone-based 1,2,3-triazoles and their respective phenazine derivatives, besides aryl triazoles. We also outline the evaluation these new derivatives against pan-susceptible *M. tuberculosis* $H_{37}Rv$ (ATCC 27294).

Results and Discussion

Initially, β-lapachone-based 1,2,3-triazoles **6**-**10** were prepared from lapachol (**1**) (Scheme 1). As previously described,[22] lapachol (**1**) underwent cyclisation to β-lapachone (**2**) in the presence of H_2SO_4. Compound **2** was reacted with *N*-bromosuccinimide (NBS) in CCl_4, with benzoyl peroxide as an initiator, to produce 3,4-dibromo-β-lapachone (**3**).[20] In the next step, **3** was stirred overnight with sodium azide in dichloromethane, to prepare **4** as previously described.[20] Two major products were obtained: 3-bromo-4-azide-α-lapachone and 3-bromo-4-azide-β-lapachone (**4**). Key intermediate **4** was isolated by column chromatography and used to prepare the respective β-lapachone-based 1,2,3-triazoles **6**-**10**.[20] Cu-catalyzed azide-alkyne cycloaddition (CuAAC),[23] a well-established click chemistry reaction that employs a Cu(I) source, was used to produce the desired 1,2,3-triazoles, as shown in Scheme 1. The final step involved reaction of **6**-**10** with *ortho*-phenylenediamine in the presence of sodium acetate and acetic acid to obtain the phenazine compounds **11**-**15**. The same conditions were applied to key intermediate **4**, and phenazine **5** was generated in good yield. Compounds **5**-**15** were obtained in racemic form, but the *trans*-stereochemistry was confirmed by X-ray crystallography analysis of compound **12** and by comparison with previously reported data.[20]

The second group of compounds was obtained from 3-azido-*nor*-β-lapachone (**17**) following a previously described procedure.[24] Initially, 1,2,3-triazolic naphthoquinone derivatives possessing either aryl groups **19**-**24**[13,24] or alkyl groups **31**-**34**[25] were prepared (Scheme 2). To evaluate redox centre modification, the respective phenazines were prepared by the methodology described above, and novel compounds **25**-**30** and **35**-**38** were obtained in high yields (Scheme 2).

A new class of naphthoquinoidal and phenazine compounds, containing a pendant 1,2,3-triazole motif, was prepared from C-allyl lawsone (Scheme 3). The first step involved iodination to provide compound **40** using methodology described by Pinto and co-workers.[26] This reaction generates two regioisomeric products (*ortho* and *para* isomers), which were separated by column chromatography; only *ortho* isomer **40** was used for subsequent studies. Reaction of **40** with sodium azide in dimethylformamide gave the corresponding azide **41** in high yield. CuAAC was used to prepare the new naphthoquinone-based 1,2,3-triazole **42**. The reaction was accomplished using classic click chemistry conditions with phenylacetylene, $CuSO_4{\cdot}5H_2O$ as catalyst and sodium ascorbate as the reducing agent, in CH_2Cl_2:H_2O (1:1). The final step was the preparation of the respective phenazine by the reaction of **42** with *ortho*-phenylenediamine in the presence of sodium acetate and acetic acid.



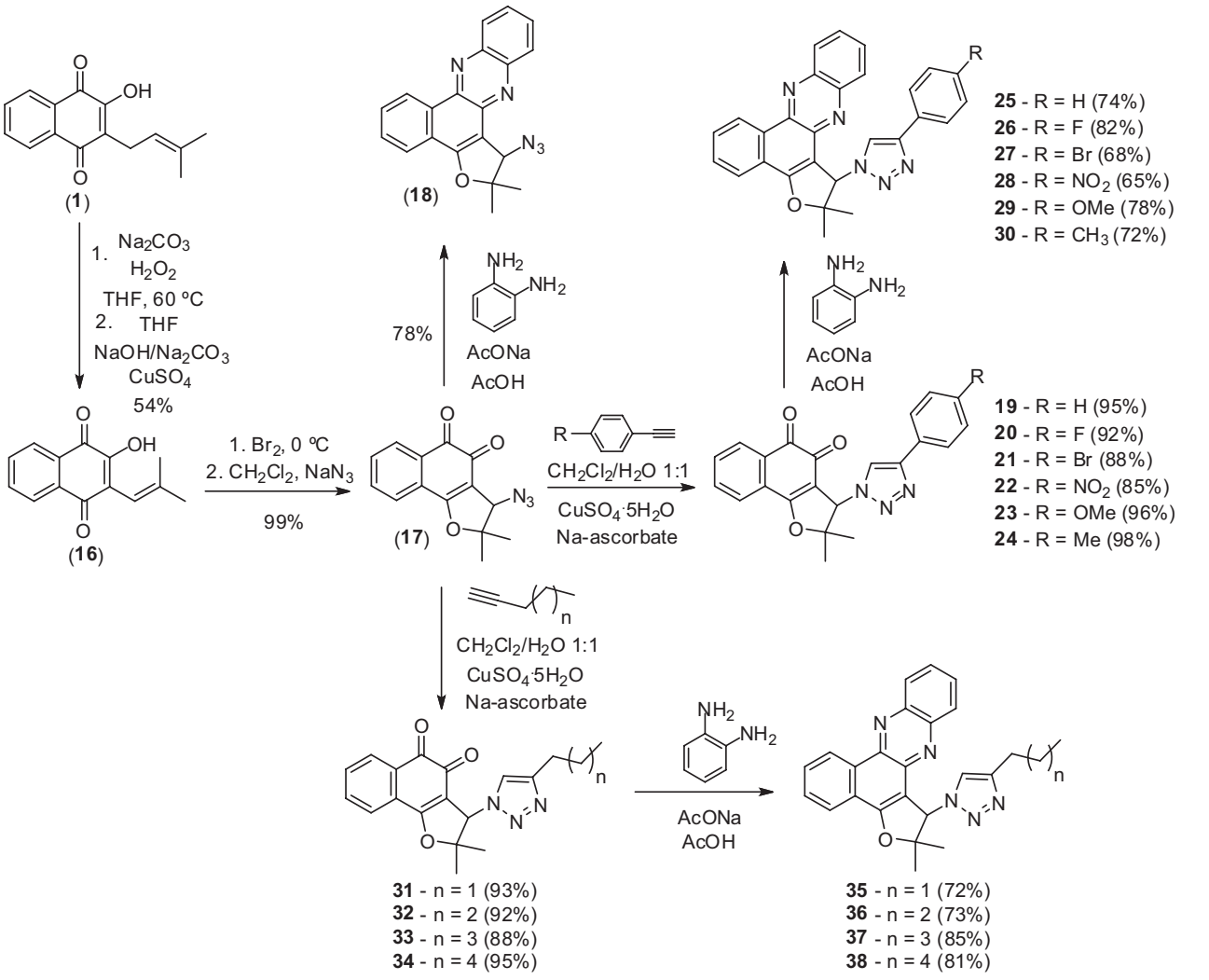
Scheme 1. Synthetic route used to prepare novel phenazine compounds **5**, **11-15**.

In the last few years, the synthesis and evaluation against TB of nitrophenyl-triazoles were described and these compounds exhibited remarkable activities.[27] Bearing in mind the potential antimicrobial activity of these structures, the last class of compounds described herein was obtained by reaction of azide derivative **44** with a range of alkynes (Scheme 4). Our aim was to obtain 1,2,3-triazoles that possess an aryl-nitro group at N-1 and diverse substituted aryl or alkyl groups at C-4. Compounds **45**-**59** were easily obtained as crystalline solids (Scheme 4) and evaluated against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294). Compounds **45**-**47** and **51**-**53** are described herein for the first time. Spectroscopic data for all previously published 1,2,3-triazoles **48**-**50** and **54**-**59** are in agreement with the data reported in the literature.[28-32]

The structures of all novel compounds were determined by infrared (IR) and ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopies. Electrospray ionization mass spectra data was also obtained. Selected compounds were recrystallised, and crystals of **12**, **19**, and **29** obtained were suitable for X-ray crystallographic analysis. The ORTEP-3 projections are shown in Figure 2, and Table S1 (Supplementary Information) lists the main crystallographic parameters. For compounds **27** and **42**, only ^{1}H NMR spectra were obtained due to the low solubility of these derivatives.

Our research group has recently described quinoidal compounds with potent activity against neglected diseases, such as leishmaniasis,[12] tuberculosis,[17,18] and Chagas disease.[13,24] As a continuation of our screening programme for the discovery of novel antimycobacterial compounds, we describe here the synthesis of a series of naphthoquinones and their phenazine derivatives, as well as the evaluation of these compounds against *Mycobacterium tuberculosis* $H_{37}Rv$.

The structures were designed based on the activities previously reported for β-lapachone and their phenazine

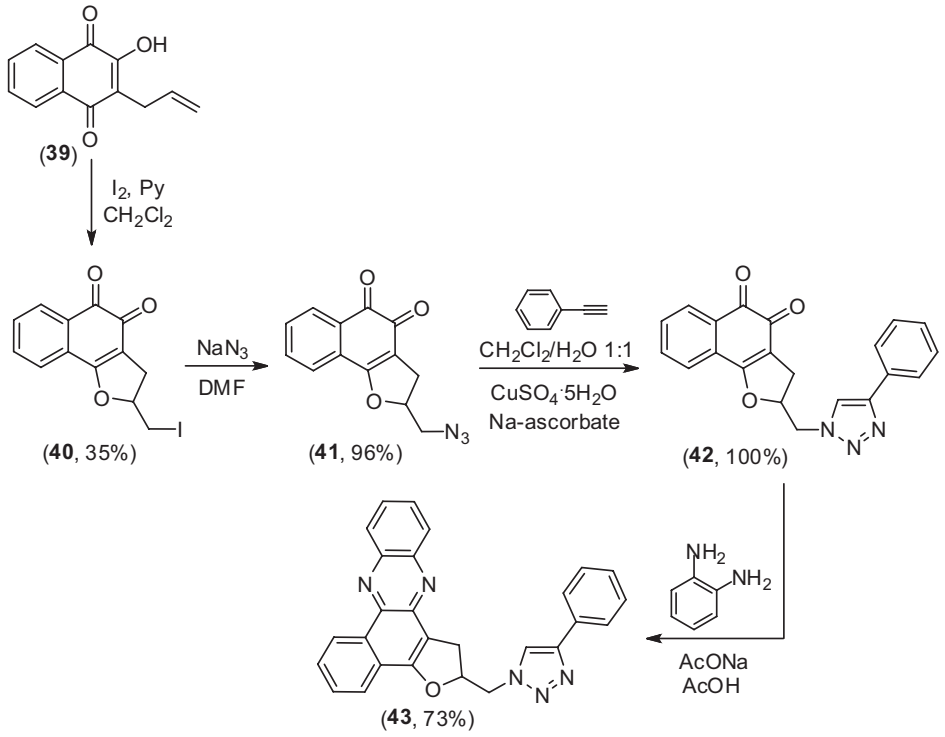


Scheme 2. Synthetic route used to prepare *nor*-β-lapachone-based 1,2,3-triazoles and their phenazine derivatives.

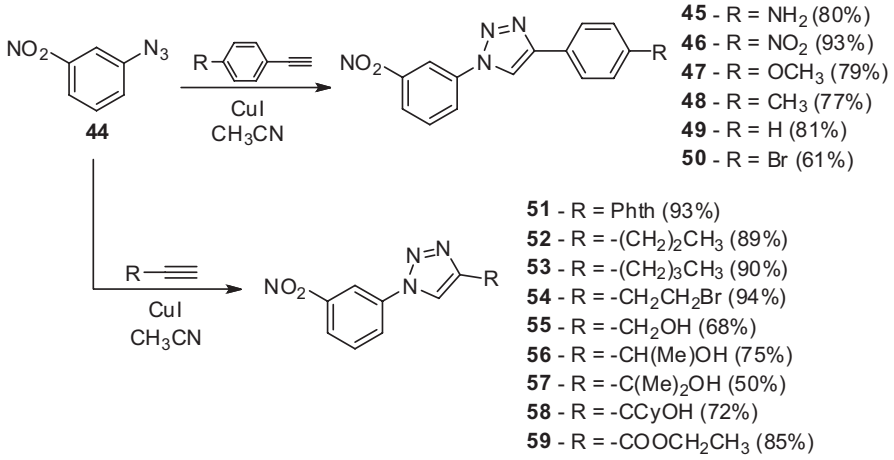
derivatives against $H_{37}Rv$ strain of *M. tuberculosis*,[34] as illustrated in the Scheme 5. The compound β-lapachone (**2**) presented activity against both susceptible and resistant strains of TB[34] and this molecule represents an important starting point for the synthesis of new compounds. As recently published by our group,[15] redox centre and C-ring modifications in prototype **2** are important strategies used in the preparation of compounds with diverse biological activities. These strategies were used with success in the synthesis of anti-TB compounds from β-lapachone (**2**) as previously described (Scheme 5).[34] Based on these principles, 1,2,3-triazole heterocyclic rings were coupled to the C-ring of lapachones (Scheme 5). The incorporation of this class of heterocyclic ring was successful in the preparation of trypanocidal and leishmanicidal compounds.[12,13,33] Another important example of molecular hybridization[35] was recently reported by Pyta *et al.*[36] Hybrids were prepared by the coupling of triazole to 3-formylrifamycin moieties and the reported compounds presented antibacterial and antitubercular properties.

Finally, by using the strategy of redox centre modification, the phenazine derivatives were prepared (Scheme 5). As discussed before, this class of compounds presents activity against *M. tuberculosis* and is also a subject of our study.

The first class of compounds evaluated were phenazines **5** and **11**-**15** and their precursors quinones **6**-**10** (Table 1). Low activities were observed for the phenazine derivatives, with average MIC values = 100 μg mL^{-1} or > 200 μg mL^{-1}, indicating that incorporation of the 1,2,3-triazole in the presence of the phenazine moiety was not effective from the biological point of view. A hypothesis for observation is that the presence of the 1,2,3-triazole in the C-ring of phenazines could hinder the penetration of the compound into the lipid mycobacterial membrane. In contrast, potent activities were observed for β-lapachone-based 1,2,3-triazoles **6**-**10**, with MIC values ≤ 6.25 μg mL^{-1}, and



Scheme 3. Synthesis of phenazine **43** from C-allyl lawsone (**39**).



Scheme 4. Synthesis of 1,2,3-triazoles from azide derivative **44**.

these structures were considered important prototypes to further studies against TB.

Differences between the β-lapachone (dihydropyran ring) *versus nor*-β-lapachone derivatives (dihydrofuran ring) were also investigated. Initially, phenazines **25**-**30** were prepared which possess an aryl ring with either electron withdrawing or donating groups. As observed for phenazines **11-15**, compounds **25**-**30** were also inactive, with a majority having MIC values > 200 μg mL^{-1} (Table 1). Finally, quinones **21**, **22**, and **24** showed moderate activity against TB, with MIC values of 12 μg mL^{-1}; the value observed for **19** was ≤ 6.25 μg mL^{-1}, highlighting the potential of this structure (Table 1).

With the aim of improving bacillus membrane lipid penetration, we planned the synthesis of phenazines **35**-**38,** which are modified with linear aliphatic substituents. Unfortunately, our strategy was not successful, and compounds **35**-**38** were also inactive against *M. tuberculosis*, with MIC values = 100 μg mL^{-1}. As observed for the β-lapachone derivatives, the quinones used to prepare the respective phenazines, **35**-**38**, presented MIC values in the range of 12.5-25 μg mL^{-1} (Table 1).

In the case of naphthoquinoidal compounds, the importance of the dihydropyran ring for biological activitity was highlighted, as compounds **6**-**10** (MIC value ≤ 6.25 μg mL^{-1}) showed generally stronger activities

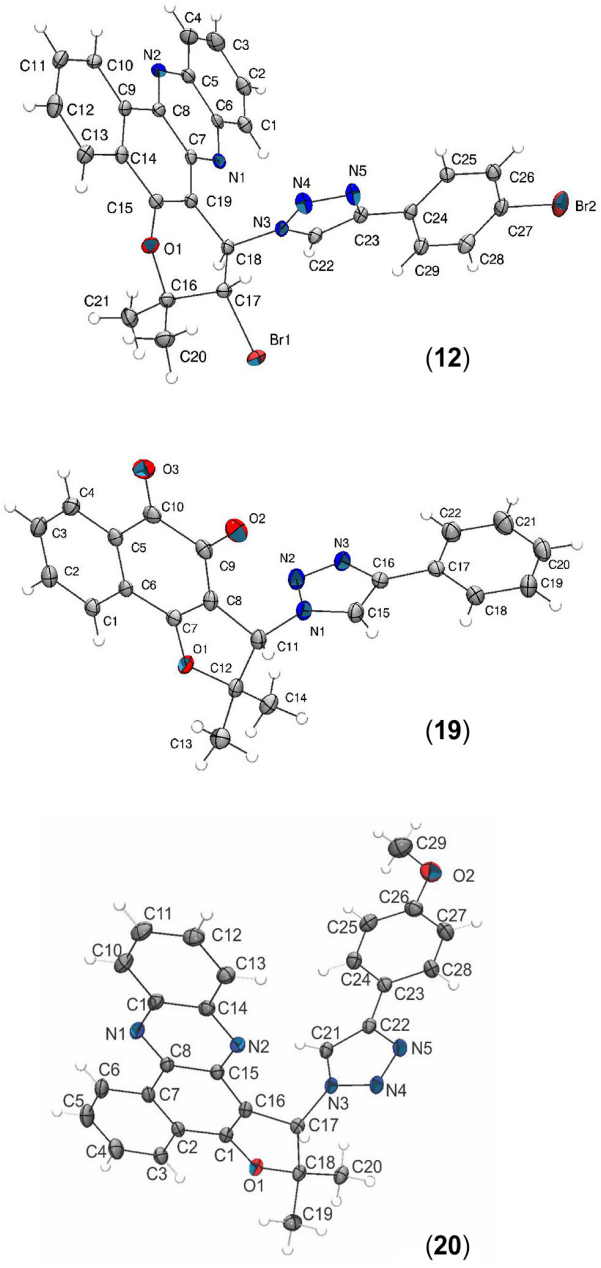


Figure 2. ORTEP-3 projections of molecules **12**, **19** and **29** showing the atom-numbering and displacement ellipsoids at the 20% (for **12** and **19**) and 50% (**29**) probability level.

compared to the respective *nor*-β-lapachone derivatives **21**, **22**, **24**, **33** and **34**, with MIC values ≤ 12.5 μg mL^{-1} (Table 1).

Lapachones prepared from C-allyl lawsone (**39**) represent an unexplored class of substances with potential activities. Recently, we described the antitumor properties of iodinated and methylated naphthoquinones synthesized from **39**.[37] Coelho *et al.*[34] reported that the phenazine obtained from **40** has an MIC value > 100 μg mL^{-1} (Scheme 6). Herein, we described the synthesis and evaluation against *M. tuberculosis* $H_{37}Rv$ of compound **43**, obtained by C-ring modification of compound **40**. Our strategy, based on the molecular hybridization by appendage of a 1,2,3-triazole, was not effective since the new phenazine **43** was also inactive (MIC > 200 μg mL^{-1}) (Scheme 6).

Although the phenazines were not active against TB, the quinones described herein showed potential as effective anti-TB agents and these structures represent an important starting point for the development of new drugs. For instance, strategies for structural modification, such as molecular hybridization with potent antimycobacterial moieties, could be considered to improve the activity of the naphthoquinones **5**-**10**, which have MIC values ≤ 6.25 μg mL^{-1}.

Finally, we also undertook the pharmacological evaluation of 1,2,3-triazoles (**45**-**59**), which do not possess a quinoidal system. Unfortunately, these compounds were inactive with MIC values > 100 μg mL^{-1} (Table 1).

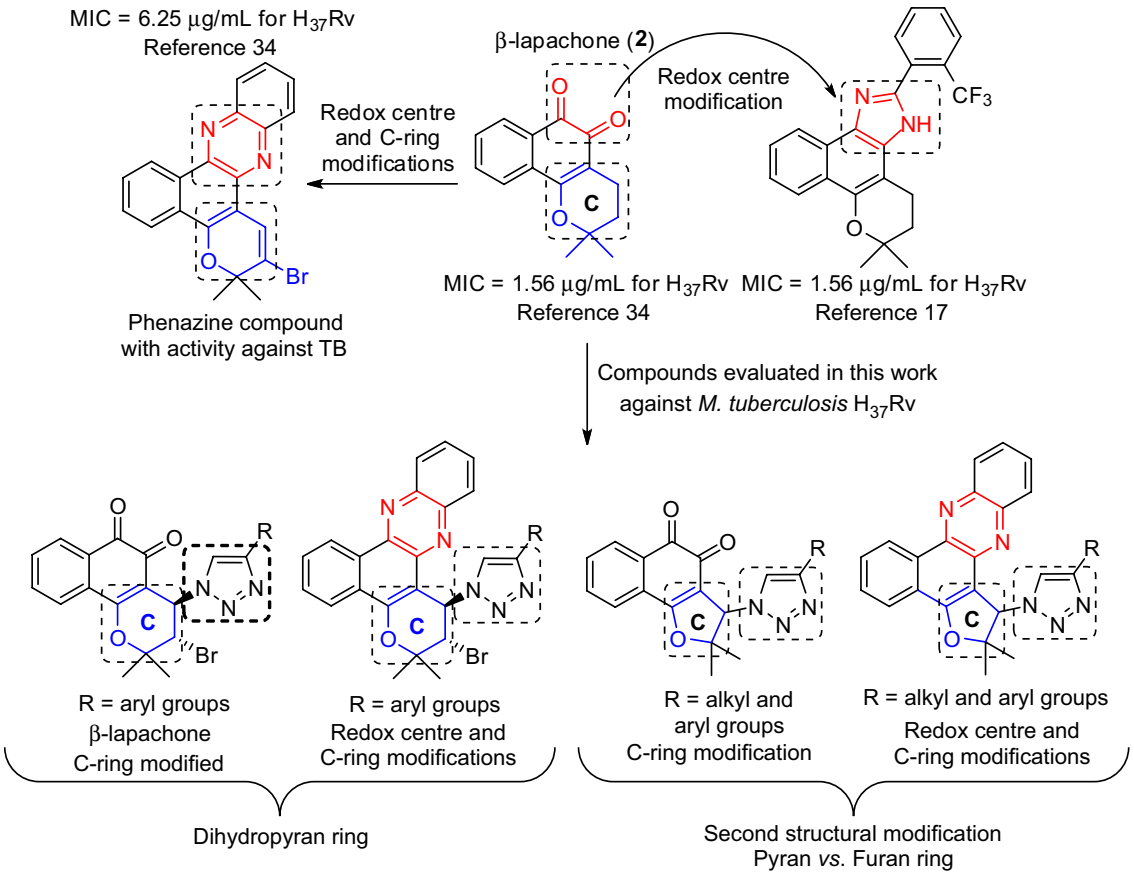
Conclusions

Twenty five novel compounds are described herein, and forty-six substances were evaluated against *M. tuberculosis* $H_{37}Rv$. Among these structures, six compounds are considered to be potential antimycobacterial agents, with MIC values ≤ 6.25 μg mL^{-1}. These compounds were obtained from lapachol, an abundant natural product, using a simple synthetic route, representing a facile strategy to obtain anti-TB drugs. As part of our programme to identify novel drugs, the compounds described here will be modified further to obtain compounds that are more active than drugs currently used in the therapeutic fight against tuberculosis.

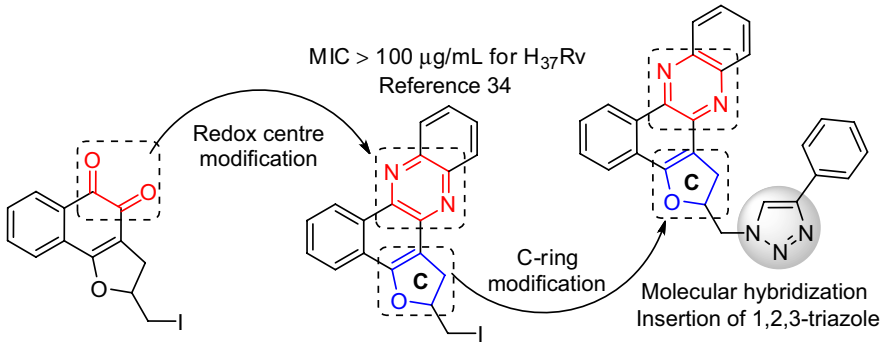
Experimental

Chemistry

Melting points were obtained on Thomas Hoover apparatus and are uncorrected. Analytical grade solvents were used. Column chromatography was performed on silica gel (Acros Organics, 0.035-0.070 mm, pore diameter ca. 6 nm). Infrared spectra were recorded on a Shimadzu IR Prestige-21 Fourier transform infrared (FTIR) spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at room temperature using a Varian Unity Plus 300, Bruker AVANCE DPX200 and AVANCE DRX400, in the solvents indicated, with tetramethylsilane (TMS) as internal reference. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hertz. Mass spectra (electrospray ionization) were obtained using a MicroTOF Ic (Bruker



Scheme 5. Structures of the compounds evaluated against *M. tuberculosis*.



Scheme 6. Strategy used for the design of the compound **43**.

Daltonics). For the mass spectra analysis, methanol was used as solvent. Some parameters: positive ion mode, acquisition *m/z*: 200.0000-700.0000, event time: 300 ms and ion accumulation: 10.00 ms.

Preparation of the synthetic precursors **1**, **2**, **3** and **16**

Lapachol (**1**) was extracted from the heartwood of *Tabebuia sp.* (*Tecoma*) and purified by a series of recrystallizations. The compound β-lapachone (**2**) was prepared from **1**, by reaction with sulfuric acid, and used to prepare the respective bromine derivative, 3,4-dibromo-β-lapachone (**3**), as previously reported.[20] From lapachol (**1**), *nor*-lapachol (**16**) was prepared in two steps using Hooker oxidation.[38]

Synthetic procedure to prepare the phenazine compounds

All the phenazines **5**, **11**-**15**, **25**-**30**, **35**-**38** and **43** were prepared according to the classical methodology described by Hooker[39] from the reaction of the appropriated quinones with *ortho*-phenylenediamine. All compounds are described here for the first time with exception of compound **25**.[33] A mixture of the quinone (0.5 mmol), sodium acetate

Table 1. MIC of the tested compounds against *Mycobacterium tuberculosis* $H_{37}Rv$

Compound	Classes of the evaluated compound	MIC / (μg mL^{-1})
5	Phenazine (dihydropyran ring)	> 200
6	β-Lapachone-based 1,2,3-triazole (quinone)	≤ 6.25
7	β-Lapachone-based 1,2,3-triazole (quinone)	≤ 6.25
8	β-Lapachone-based 1,2,3-triazole (quinone)	≤ 6.25
9	β-Lapachone-based 1,2,3-triazole (quinone)	≤ 6.25
10	β-Lapachone-based 1,2,3-triazole (quinone)	≤ 6.25
11	Phenazine (dihydropyran ring)	100
12	Phenazine (dihydropyran ring)	> 200
13	Phenazine (dihydropyran ring)	> 200
14	Phenazine (dihydropyran ring)	> 200
15	Phenazine (dihydropyran ring)	> 200
18	Phenazine (dihydrofuran ring)	25
19	*nor*-β-Lapachone-based 1,2,3-triazole (quinone)	≤ 6.25
20	*nor*-β-Lapachone-based 1,2,3-triazole (quinone)	nd
21	*nor*-β-Lapachone-based 1,2,3-triazole (quinone)	12.5
22	*nor*-β-Lapachone-based 1,2,3-triazole (quinone)	12.5
23	*nor*-β-Lapachone-based 1,2,3-triazole (quinone)	nd
24	*nor*-β-Lapachone-based 1,2,3-triazole (quinone)	12.5
25	Phenazine (dihydrofuran ring)	100
26	Phenazine (dihydrofuran ring)	> 200
27	Phenazine (dihydrofuran ring)	> 200
28	Phenazine (dihydrofuran ring)	> 200
29	Phenazine (dihydrofuran ring)	> 200
30	Phenazine (dihydrofuran ring)	100
31	*nor*-β-Lapachone-based 1,2,3-triazole (quinone)	25
32	*nor*-β-Lapachone-based 1,2,3-triazole (quinone)	25
33	*nor*-β-lapachone-based 1,2,3-triazole (Quinone)	12.5
34	*nor*-β-Lapachone-based 1,2,3-triazole (quinone)	12.5
35	Phenazine (dihydrofuran ring)	100
36	Phenazine (dihydrofuran ring)	100
37	Phenazine (dihydrofuran ring)	100
38	Phenazine (dihydrofuran ring)	100
43	Phenazine (dihydrofuran ring)	> 200
45	Nitrophenyl triazole	> 200
46	Nitrophenyl triazole	> 200
47	Nitrophenyl triazole	> 200
48	Nitrophenyl triazole	> 200
49	Nitrophenyl triazole	> 200
50	Nitrophenyl triazole	> 200
51	Nitrophenyl triazole	200
52	Nitrophenyl triazole	200
53	Nitrophenyl triazole	200
54	Nitrophenyl triazole	100
55	Nitrophenyl triazole	100
56	Nitrophenyl triazole	50
57	Nitrophenyl triazole	> 200
58	Nitrophenyl triazole	> 200
59	Nitrophenyl triazole	100
Etambutol		4
Streptomycin		1

nd: not determined.

(0.95 mmol), *ortho*-phenylenediamine (0.55 mmol) in 3 mL of glacial acetic acid was stirred and monitored by silica gel thin-layer chromatography (TLC). After, the crude reaction product was poured into water and the precipitate formed was filtrate and then purified in silica gel chromatography, using a mixture of hexane-ethyl acetate, increasing polarity. In the case that did not form precipitate, the residue was extracted with organic solvent, dried over anhydrous sodium sulfate, followed by concentration under vacuum and purification by column chromatography.

1-Azido-2-bromo-3,3-dimethyl-2,3-dihydro-1*H*-benzo[a]pyrano[2,3-c]phenazine (**5**)

The reaction of compound **4** (181 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.55 mmol) in the presence of sodium acetate (78 mg, 0.95 mmol) in 3 mL of acetic acid yielded product **5**, (167 mg, 0.360 mmol, 72% yield), as a yellow solid; mp 154-156 ºC; IR (KBr) ν / cm^{-1} 2102 (N_3), 1633 (C=N), 3061 (C=C), 760 (Ar–CH_3), 2975 (C–H); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.36 (d, 1H, *J* 7.2 Hz), 8.43-8.19 (3H, m), 7.94-7.72 (4H, m), 5.80 (d, 1H, *J* 5.5 Hz), 4.48 (d, 1H, *J* 5.5 Hz), 2.08 (3H, s), 1.80 (3H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.2, 142.1, 140.8, 140.6, 140.0, 131.6, 129.8, 129.4, 129.8, 128.8, 125.2, 122.0, 107.9, 107.3, 83.2, 79.0, 66.9, 61.4, 57.0, 26.2, 24.2; ESI-MS *m/z*, calcd. for $[C_{21}H_{16}BrN_5OH^+]$: 434.0616; found: 434.1029.

2-Bromo-3,3-dimethyl-1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-2,3-dihydro-1*H*-benzo[a]pyrano[2,3-c]phenazine (**11**)

The reaction of compound **6** (232 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.55 mmol) in the presence of sodium acetate (78 mg, 0.95 mmol) in 3 mL of acetic acid yielded product **11**, (219 mg, 0.410 mmol, 82% yield), as a yellow solid; mp 249-250 ºC; IR (KBr) ν / cm^{-1} 1603 (C=N), 3133 (C=C), 760 (Ar–CH_3), 2912 (C–H); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.26 (d, 1H, *J* 6.5 Hz), 8.30 (d, 1H, *J* 8.8 Hz), 8.17-8.12 (1H, m), 8.08 (1H, s), 7.89-7.71 (5H, m), 7.67-7.51 (2H, m), 7.34-7.18 (3H, m), 6.60 (d, 1H, *J* 8.1 Hz), 5.16 (d, 1H, *J* 8.1 Hz), 1.70 (3H, s), 1.65 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.2, 146.5, 142.3, 142.1, 140.7, 140.2, 132.2, 131.0, 130.3, 130.2, 129.7, 129.6, 129.3, 128.9, 128.8, 128.1, 125.9, 125.5, 123.4, 122.6, 106.6, 80.8, 61.2, 57.2, 27.7, 21.3; ESI-MS *m/z*, calcd. for $[C_{29}H_{22}BrN_5OH^+]$: 536.10861; found: 536.1193.

2-Bromo-1-(4-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl)-3,3-dimethyl-2,3-dihydro-1*H*-benzo[a]pyrano[2,3-c]phenazine (**12**)

The reaction of compound **7** (271 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.55 mmol) in the

presence of sodium acetate (78 mg, 0.95 mmol) in 3 mL of acetic acid yielded product **12**, (201 mg, 0.375 mmol, 75% yield), as a yellow solid; mp 232-235 ºC; IR (KBr) ν / cm^{-1} 1633 (C=N), 3124 (C=C), 773 (Ar–CH_3), 2922 (C–H); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.35 (d, 1H, *J* 9.1 Hz), 8.41-8.36 (1H, m), 8.29-8.20 (1H, m), 8.19 (1H, s), 7.93-7.78 (3H, m), 7.75-7.62 (4H, m), 7.57-7.46 (2H, m), 6.66 (d, 1H, *J* 8.3 Hz), 5.21 (d, 1H, *J* 8.3 Hz), 1.80 (3H, s), 1.73 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.2, 146.5, 143.3, 143.2, 141.7, 141.2, 133.2, 131.5, 131.3, 130.9, 130.8, 130.7, 130.3, 129.8, 129.1, 128.5, 126.7, 124.5, 123.8, 122.9, 107.6, 81.9, 62.4, 58.3, 28.8, 22.7.

2-Bromo-1-(4-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl)-3,3-dimethyl-2,3-dihydro-1*H*-benzo[a]pyrano[2,3-c]phenazine (**13**)

The reaction of compound **8** (241 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.95 mmol) in 3 mL of acetic acid yielded product **13**, (216 mg, 0.390 mmol, 78% yield), as a yellow solid; mp 263-264 ºC; IR (KBr) ν / cm^{-1} 1484 (C=N), 2915 (C=C–H), 776 (Ar–CH_3), 3127 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$/DMSO) δ 9.34 (d, 1H, *J* 9.0 Hz), 8.39 (d, 1H, *J* 9.0 Hz), 8.24 (1H, s), 8.22 (d, 1H, *J* 7.8 Hz), 7.89-7.81 (3H, m), 7.80-7.67 (4H, m), 7.07 (t, 2H, *J* 8.6 Hz), 6.67 (d, 1H, *J* 8.5 Hz), 5.20 (d, 1H, *J* 8.4 Hz), 1.82 (3H, s), 1.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO) δ 161.2 (246.5 Hz, d) 152.9, 145.3, 142.0, 141.8, 140.4, 139.9, 131.8, 130.1, 130.0, 129.6, 129.4, 129.1, 128.5, 127.8, 127.3 (*J* 8.0 Hz, d), 127.1 (*J* 3.0 Hz, d), 125.2, 123.2, 122.4, 115.7 (*J* 21.6 Hz, d), 106.5, 80.8, 61.0, 57.2, 27.7, 20.7; ESI-MS *m/z*, calcd. for [$C_{29}H_{21}BrFN_5OH^+$]: 554.0991; found: 554.1006.

2-Bromo-1-(4-(4-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-3,3-dimethyl-2,3-dihydro-1*H*-benzo[a]pyrano[2,3-c]phenazine (**14**)

The reaction of compound **9** (247 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.95 mmol) in 3 mL of acetic acid yielded product **14**, (232 mg, 0.410 mmol, 82% yield), as a yellow solid; mp 248-249 ºC; IR (KBr) ν / cm^{-1} 1494 (C=N), 2981 (C=C), 1252 (Ar–O–CH_3), 3124 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$/DMSO) δ 9.30 (d, 1H, *J* 6.1 Hz), 8.36 (d, 1H, *J* 7.2 Hz), 8.19-8.16 (1H, m), 8.16 (1H, s), 7.85-7.81 (3H, m), 7.73-7.63 (4H, m), 6.90 (d, 2H, *J* 8.6 Hz), 6.65 (d, 1H, *J* 8.3 Hz), 5.20 (d, 1H, *J* 8.3 Hz), 3.78 (3H, s), 1.78 (3H, s), 1.71 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO) δ 159.6, 153.0, 149.8, 146.3, 142.3, 142.1, 140.6, 140.1, 136.4, 130.0, 130.2, 129.7, 129.6, 129.2, 128.7, 128.1, 127.1, 125.5, 124.0, 123.7, 123.4, 122.1, 114.4, 106.8, 80.9, 61.1, 57.5, 55.5, 27.8, 21.1; ESI-MS *m/z*, calcd. for [$C_{30}H_{24}BrN_5O_2H^+$]: 566.1299; found: 566.1226.

2-Bromo-3,3-dimethyl-1-(4-(p-tolyl)-1*H*-1,2,3-triazol-1-yl)-2,3-dihydro-1*H*-benzo[a]pyrano[2,3-c]phenazine (**15**)

The reaction of compound **10** (239 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.5 mmol) in 3 mL of acetic acid yielded product **15**, (211 mg, 0.385 mmol, 77% yield), as a yellow solid; mp 246-248 ºC; IR (KBr) ν / cm^{-1} 1418 (C=N), 2915 (C=C), 770 (Ar–CH_3), 3127 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$/DMSO) δ 9.33 (d, 1H, *J* 8.5 Hz), 8.38 (d, 1H, *J* 7.0 Hz), 8.21 (d, 1H, *J* 7.6 Hz), 8.16 (1H, s), 7.94-7.81 (3H, m), 7.73-7.68 (4H, m), 7.18 (d, 2H, *J* 8.0 Hz), 6.65 (d, 1H, *J* 8.3 Hz), 5.21 (d, 1H, *J* 8.3 Hz), 2.34 (3H, s), 1.78 (3H, s), 1.72 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO) δ 153.1, 146.6, 142.3, 142.1, 140,7, 140.1, 137.9, 132.1, 130.3, 130.3, 129.7, 129.6, 129.3, 128.8, 128.2, 128.1, 125.8, 125.5, 123.4, 122.4, 106.8, 80.9, 61.2, 57.4, 27.8, 21.5, 21.1; ESI-MS *m/z*, calcd. for [$C_{30}H_{24}BrN_5OH^+$]: 550.1242; found: 550.1207.

1-(4-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl)-2,2-dimethyl-1,2-dihydrobenzo[a]furo[2,3-c]phenazine (**26**)

The reaction of compound **20** (194 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.5 mmol) in 3 mL of acetic acid yielded product **26**, (189 mg, 0.410 mmol, 82% yield), as a yellow solid; mp 291-293 ºC; IR (KBr) ν / cm^{-1} 1596 (C=N), 3091 (C=C), 1428 (C–F), 3412 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, 1H, *J* 8.0 Hz), 8.29-8.24 (1H, m), 8.21 (d, 1H, *J* 7.7 Hz), 8.03-7.98 (1H, m), 7.93 (t, 1H, *J* 7.5 Hz), 7.86 (t, 1H, *J* 7.2 Hz), 7.76-7.71 (2H, m), 7.65-7.59 (2H, m), 7.28 (1H, s), 6.95 (t, 2H, *J* 8.5 Hz), 6.70 (1H, s), 1.83 (3H, s), 1.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, *J* 246.7 Hz), 160.2, 146.5, 142.8, 141.6, 140.9, 140.5, 133.4, 130.3, 130.0 (d, *J* 6.8 Hz), 129.7, 129.0, 128.8, 127.4, 127.3, 126.7 (d, *J* 3.2 Hz), 126.2, 124.1, 123.2, 118.6, 115.5 (d, *J* 21.7 Hz), 108.8, 92.8, 68.7, 27.9, 21.5; ESI-MS *m/z*, calcd. for [$C_{28}H_{20}FN_5OH^+$]: 462.1730; found: 462.1697.

1-(4-(4-Bromophenyl)-1*H*-1,2,3-triazol-1-yl)-2,2-dimethyl-1,2-dihydrobenzo[a]furo[2,3-c]phenazine (**27**)

The reaction of compound **21** (225 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.5 mmol) in 3 mL of acetic acid yielded product **27**, (177 mg, 0.340 mmol, 68% yield), as a yellow solid; mp 297-299 ºC; IR (KBr) ν / cm^{-1} 1596 (C=N), 2988 (C=C), 1047 (C–Br), 3081 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, 1H, *J* 7.5 Hz), 8.29 (d, 1H, *J* 5.1 Hz), 8.23 (d, 1H, *J* 7.7 Hz), 8.11-8.06 (1H, m), 7.93

(dt, 2H, *J* 26.2, 7.2 Hz), 7.82-7.70 (2H, m), 7.55 (d, 2H, *J* 8.3 Hz), 7.41 (d, 2H, *J* 8.3 Hz), 7.33 (1H, s), 6.72 (1H, s), 1.83 (3H, s), 1.35 (3H, s). ESI-MS *m/z*, calcd. for $[C_{28}H_{20}BrN_5OH^+]$: 522.0798; found: 522.0800.

2,2-Dimethyl-1-(4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl)-1,2-dihydrobenzo[a]furo[2,3-c]phenazine (**28**)

The reaction of compound **22** (208 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.5 mmol) in 3 mL of acetic acid yielded product **28**, (158 mg, 0.325 mmol, 65% yield), as a yellow solid; mp 289-291 ºC; IR (KBr) ν / cm^{-1} 1336 (NO_2), 1517 (C–NO_2), 3073 (C=C), 756 (Ar–NO_2), 3412 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, 1H, *J* 8.3 Hz), 8.28-7.84 (8H, m), 7.78-7.58 (3H, m), 7.48 (1H, s), 6.76 (1H, s), 1.38 (3H, s), 1.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO) δ 160.2, 146.8, 144.8, 142.4, 140.2, 129.8, 129.5, 128.6, 128.5, 128.5, 126.0, 125.9, 123.9, 123.8, 123.1, 113.8, 108.3, 92.5, 92.5, 68.7, 68.4, 55.0, 29.4, 27.4, 21.4; ESI-MS *m/z*, calcd. for $[C_{28}H_{20}N_6O_3H^+]$: 489.1675; found: 489.1655.

1-(4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-2,2-dimethyl-1,2-dihydrobenzo[a]furo[2,3-c]phenazine (**29**)

The reaction of compound **23** (200 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.5 mmol) in 3 mL of acetic acid yielded product **29**, (184 mg, 0.39 mmol, 78% yield), as a yellow solid; mp 269-270 ºC; IR (KBr) ν / cm^{-1} 1597 (C=N), 3094 (C=C), 1247 (Ar–O–CH_3), 3413 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, 1H, *J* 8.0 Hz), 8.34-8.19 (2H, m), 8.08-7.84 (4H, m), 7.80-7.70 (2H, m), 7.66-7.54 (2H, m), 6.81 (d, 2H, *J* 8.5 Hz), 6.72 (1H, s), 3.74 (3H, s), 1.83 (3H, s), 1.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 159.4, 147.2, 142.6, 141.6, 140.9, 140.4, 130.2, 129.9, 129.8, 129.6, 128.9, 128.8, 126.9, 126.2, 124.1, 123.2, 118.0, 114.0, 108.9, 92.9, 68.6, 55.2, 27.9, 21.5; ESI-MS *m/z*, calcd. for $[C_{29}H_{23}N_5O_2H^+]$: 474.1930; found: 474.1897.

2,2-Dimethyl-1-(4-(p-tolyl)-1*H*-1,2,3-triazol-1-yl)-1,2-dihydrobenzo[a]furo[2,3-c]phenazine (**30**)

The reaction of compound **24** (192 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.5 mmol) in 3 mL of acetic acid yielded product **30**, (164 mg, 0.360 mmol, 72% yield), as a yellow solid; mp 269-271 ºC; IR (KBr) ν / cm^{-1} 1633 (C=N), 3095 (C=C), 756 (Ar–CH3), 3413 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (d, 1H, *J* 6.9 Hz), 8.30-8.21 (2H, m), 8.08-7.83 (3H, m), 7.79-7.69 (2H, m), 7.62-7.51 (2H, m), 7.31 (1H, s), 7.08 (d, 2H, *J* 6.3 Hz), 6.72 (1H, s), 2.28 (3H, s), 1.83 (3H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 142.7, 141.6, 140.8, 140.4, 137.8, 133.3, 130.2, 129.9, 129.8, 129.6, 129.3, 129.0, 128.8, 127.7, 126.2, 125.4, 124.1, 123.2, 118.5, 108.8, 92.8, 68.7, 29.7, 27.5, 21.5, 21.1; ESI-MS *m/z*, calcd. for $[C_{29}H_{23}N_5OH^+]$: 458.1902; found: 458.1950.

2,2-Dimethyl-1-(4-propyl-1*H*-1,2,3-triazol-1-yl)-1,2-dihydrobenzo[a]furo[2,3-c]phenazine (**35**)

The reaction of compound **31** (168 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.5 mmol) in 3 mL of acetic acid yielded product **35**, (147 mg, 0.360 mmol, 72% yield), as a yellow solid; mp 278-280 ºC; IR (KBr) ν / cm^{-1} 1596 (C=N), 2925 (C=C), 753 (Ar–CH_3), 3107 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (d, 1H, *J* 6.5 Hz), 8.32-8.24 (1H, m), 8.21 (d, 1H, *J* 6.6 Hz), 8.04-7.84 (3H, m), 7.80-7.72 (2H, m), 6.98 (1H, s), 6.62 (1H, s), 2.61-2.48 (2H, m), 1.81 (3H, s), 1.55 (dt, 2H, *J* 14.7, 7.3 Hz), 1.29 (3H, s), 0.80 (t, 3H, *J* 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 147.1, 142.1, 141.2, 140.4, 139.8, 132.6, 129.7, 129.5, 129.3, 129.2, 128.2, 128.2, 125.6, 123.6, 122.7, 119.9, 108.4, 92.2, 67.9, 27.1, 27.0, 21.9, 20.8, 13.0. ESI-MS *m/z*, calcd. for $[C_{25}H_{23}N_5OH^+]$: 410.1980; found: 410.1897.

1-(4-Butyl-1*H*-1,2,3-triazol-1-yl)-2,2-dimethyl-1,2-dihydrobenzo[a]furo[2,3-c]phenazine (**36**)

The reaction of compound **31** (175 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.5 mmol) in 3 mL of acetic acid yielded product **36**, (154 mg, 0.36 mmol, 73% yield), as a yellow solid; mp 269-270 ºC; IR (KBr) ν / cm^{-1} 1596 (C=N), 2955 (C=C), 763 (Ar–CH_3), 3071 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, 1H, *J* 7.9 Hz), 8.28 (dd, 1H, *J* 3.5, 7.3 Hz), 8.21 (d, 1H, *J* 7.6 Hz), 8.00-7.87 (3H, m), 7.81-7.76 (2H, m), 7.05 (s, 1H), 6.61 (s, 1H), 2.65-2.51 (2H, m), 1.82 (3H, s), 1.57-1.44 (2H, m), 1.29 (3H, s), 1.21 (2H, m), 0.79 (t, 3H, *J* 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 147.2, 142.0, 141.2, 140.3, 139.7, 132.5, 129.7, 129.5, 129.3, 129.1, 128.2, 123.6, 122.7, 125.6, 125.4, 119.9, 108.6, 92.1, 67.2, 30.8, 27.1, 24.7, 21.5, 20.8, 13.2; ESI-MS *m/z*, calcd. for $[C_{26}H_{25}N_5OH^+]$: 424.2137; found: 424.2099.

2,2-Dimethyl-1-(4-pentyl-1*H*-1,2,3-triazol-1-yl)-1,2-dihydrobenzo[a]furo[2,3-c]phenazine (**37**)

The reaction of compound **33** (182 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.5 mmol) in 3 mL of acetic acid yielded product **37**, (185 mg, 0.425 mmol, 85% yield), as a yellow solid; mp 261-263 ºC; IR (KBr) ν / cm^{-1} 1597

(C=N), 2958 (C=C), 760 (Ar–CH_3), 3072 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (d, 1H, *J* 7.8 Hz), 8.28 (dd, 1H, *J* 6.6, 3.1 Hz), 8.21 (d, 1H, *J* 7.6 Hz), 8.05-7.84 (3H, m), 7.77 (dd, 2H, *J* 6.6, 3.1 Hz), 7.01 (1H, s), 6.62 (1H, s), 2.67-2.47 (2H, m), 1.82 (3H, s), 1.63-1.43 (2H, m), 1.30 (3H, s), 1.24-1.11 (4H, m), 0.75 (t, 3H, *J* 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 147.6, 142.3, 141.5, 140.6, 140.0, 132.9, 129.9, 129.8, 129.6, 129.4, 128.5, 125.9, 125.8, 123.9, 123.0, 120.2, 108.7, 92.5, 68.2, 30.9, 28.6, 27.4, 25.3, 21.9, 21.1, 13.7; ESI-MS *m/z*, calcd. for $[C_{27}H_{27}N_5OH^+]$: 438.2293; found: 438.2210.

1-(4-Hexyl-1*H*-1,2,3-triazol-1-yl)-2,2-dimethyl-1,2-dihydrobenzo[a]furo[2,3-c]phenazine (**38**)

The reaction of compound **34** (189 mg, 0.5 mmol), *ortho*-phenylenediamine (60 mg, 0.5 mmol) in the presence of sodium acetate (78 mg, 0.5 mmol) in 3 mL of acetic acid yielded product **38**, (182 mg, 0.405 mmol, 81% yield), as a yellow solid; mp 259-261 ºC; IR (KBr) ν / cm^{-1} 1612 (C=N), 2955 (C=C), 763 (Ar–CH_3), 3071 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (d, 1H, *J* 7.8 Hz), 8.33-8.24 (1H, m), 8.20 (d, 1H, *J* 7.5 Hz), 8.04 (dd, 1H, *J* 6.2, 3.6 Hz), 7.90 (dt, 2H, *J* 24.8, 7.0 Hz), 7.76 (dd, 2H, *J* 6.5, 3.4 Hz), 6.84 (1H, s), 6.64 (1H, s), 2.68-2.44 (2H, m), 1.79 (3H, s), 1.53-1.42 (2H, m), 1.28 (3H, s), 1.19-1.06 (6H, m), 0.73 (t, 3H, *J* 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 148.0, 142.7, 141.7, 140.8, 140.4, 133.2, 130.1, 129.9, 129.7, 129.6, 128.9, 128.7, 126.1, 124.1, 123.2, 119.9, 109.0, 92.8, 68.4, 31.3, 29.1, 28.6, 27.5, 25.6, 22.3, 21.3, 13.8; ESI-MS *m/z*, calcd. for $[C_{28}H_{29}N_5OH^+]$: 452.2450; found: 452.2400.

2-((4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-1,2-dihydrobenzo[a]furo[2,3-c]phenazine (**43**)

The reaction of compound **42** (80 mg, 0.29 mmol), *ortho*-phenylenediamine (60 mg, 0.55 mmol) in the presence of sodium acetate (100 mg, 1.22 mmol) in 4 mL of acetic acid yielded product **43**, (88.5 mg, 0.206 mmol, 71% yield), as a yellow solid; mp 211-213 ºC; IR (KBr) ν / cm^{-1} 1638 (C=N), 763 (Ar–CH_3), 2924 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44-9.37 (1H, m), 8.33 (dd, 1H, *J* 8.1, 1.4 Hz), 8.28 (d, 1H, *J* 7.5 Hz), 8.12-8.04 (1H, m), 8.01 (1H, s), 7.90-7.76 (6H, m), 7.42 (t, 2H, *J* 7.4 Hz), 7.33 (t, 1H, *J* 7.4 Hz), 5-75-5.66 (1H, m), 4.97 (dd, 1H, *J* 14.5, 3.6 Hz), 4.83 (dd, 1H, *J* 14.5, 7.6 Hz), 4.06 (dd, 1H, *J* 15.9, 10.0 Hz), 3.67 (dd, 1H, *J* 15.9, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.00, 148.19, 141.39, 140.34, 131.91, 130.69, 130.46, 130.19, 130.16, 130.14, 130.10, 129.92, 128.91, 128.87, 128.82, 128.75, 128.74, 128.27, 126.21, 125.84, 122.10, 120.72, 83.15, 54.13, 32.06; ESI-MS *m/z*, calcd. for $[C_{27}H_{19}N_5OH^+]$: 430.1667; found: 430.1598.

2-(Azidomethyl)-2,3-dihydronaphtho[1,2-b]furan-4,5-dione (**41**)

Compound **40** (255 mg, 1.0 mmol) was stirred in presence of sodium azide (120 mg, 1.85 mmol) in 2 mL of dimethylformamide (DMF), generating product **41**, (238 mg, 0.930 mmol, 93% yield), as a red solid; mp 172-174 ºC; IR (KBr) ν / cm^{-1} 2923 (CH), 2106 (N_3), 1660 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05 (d, 1H, *J* 7.3 Hz), 7.92-7.32 (3H, m), 5.45-5.21 (1H, m), 3.84-3.49 (2H, m), 3.25 (dd, 1H, *J* 15.6, 10.1 Hz), 2.92 (dd, 1H, *J* 15.6, 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.9, 175.4, 169.4, 134.9, 132.3, 130.7, 130.3, 129.7, 127.2, 124.7, 85.8, 54.3, 29.6; ESI-MS *m/z*, calcd. for $[C_{13}H_9N_3O_3H^+]$: 256.0722; found: 256.0606.

Synthetic procedure to prepare quinone-based 1,2,3-triazoles

The substituted alkyne (0.83 mmol) was reacted with respective azide compound (0.83 mmol) in 12 mL of CH_2Cl_2/H_2O (1:1), $CuSO_4{\cdot}5H_2O$ (9.3 mg, 0.04 mmol) and sodium ascorbate (22 mg, 0.11 mmol). The mixture was agitated at room temperature until formation of the product was complete and monitored by TLC. The organic phase was extracted with CH_2Cl_2, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using a gradient mixture of hexane/ethyl acetate with increasing polarity up to 100% ethyl acetate as an eluent. Compounds **6**-**9**, **19**-**24** and **32**-**34** assayed against *M. tuberculosis* here were previously described.[12,13,20,25]

3-Bromo-2,2-dimethyl-4-(4-(p-tolyl)-1*H*-1,2,3-triazol-1-yl)-3,4-dihydro-2*H*-benzo[h]chromene-5,6-dione (**10**)

The alkyne employed was 1-ethynyl-4-methylbenzene (96 mg, 0.83 mmol) with the azide **4** (300 mg, 0.83 mmol) and the resulting compound **10** was a yellow solid (217 mg, 55% yield); mp 201-202 ºC; IR (KBr) ν / cm^{-1} 1650 (C=O), 1605 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.11 (d, 1H, *J* 7.4 Hz), 8.04 (s, 1H), 7.93 (d, 1H, *J* 7.7 Hz), 7.76-7.71 (m, 3H), 7.65-7.61 (m, 1H), 7.27-7,20 (m, 1H), 5.71 (d, 1H *J* 8.8 Hz), 5.07 (d, 1H, *J* 8.9 Hz), 2.37 (s, 3H), 1.76 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.6, 176.3, 162.4, 146.6, 137.6, 134.9, 132.0, 130.4, 130.3, 129.1, 128.9, 127.3, 125.5, 124.9, 122.1, 110.2, 83.2, 58.7, 53.9, 27.12, 20.9, 20.5; ESI-MS *m/z*, calcd. for $[C_{24}H_{20}BrN_3O_3H^+]$: 478.0766; found: 478.0579.

2,2-Dimethyl-3-(4-propyl-1*H*-1,2,3-triazol-1-yl)-2,3-dihydronaphtho[1,2-b]furan-4,5-dione (**31**)

The alkyne employed was pent-1-yne (56 mg, 0.83 mmol), with the azide **17** (223 mg, 0.83 mmol) and

the resulting compound **31** was a brown solid (260 mg, 93% yield); mp 173-176 ºC; IR (KBr) ν / cm^{-1} 1635 (C=O), 1678 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.12-7.97 (1H, m), 7.93-7.45 (4H, m), 5.86 (1H, s), 2.55 (t, 2H, *J* 7.0 Hz), 1.67 (3H, s), 1.61-1.49 (2H, m), 1.09 (3H, s), 0.82 (t, 3H, *J* 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.2, 174.6, 171.1, 148.0, 134.9, 133.2, 131.4, 129.7, 126.7, 125.6, 120.5, 111.4, 96.0, 66.6, 27.6, 27.5 22.5, 20.9, 13.7; ESI-MS *m/z*, calcd. for $[C_{19}H_{19}N_3O_3H^+]$: 338.1504; found: 338.1517.

2-((4-Phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-2,3-dihydronaphtho[1,2-b]furan-4,5-dione (**42**)

The alkyne employed was ethynylbenzene (84 mg, 0.83 mmol), with the azide **41** (211 mg, 0.83 mmol) and the resulting compound **42** was a red solid (281 mg, 95% yield); mp 187-188 ºC; IR (KBr) ν / cm^{-1} 2921 (C-H), 1621 (C=O), 1648 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 1H, *J* 7.3 Hz), 8.06-7.92 (1H, m), 7.91-7.77 (2H, m), 7.71-7.65 (1H, m), 7.61 (t, 2H, *J* 7.1 Hz), 7.49-7.41 (2H, m), 7.40-7.34 (1H, m), 5.64-5.53 (1H, m), 4.86 (dd, 1H, *J* 14.1, 2.7 Hz), 4.77 (dd, 1H, *J* 14.1, 7.0 Hz), 3.40 (dd, 1H, *J* 15.6, 10.1 Hz), 3.03 (dd, 1H, *J* 15.6, 6.9 Hz); ESI-MS *m/z*, calcd. for $[C_{21}H_{15}N_3O_3H^+]$: 358.1191; found: 358.1092.

Synthetic procedure to prepare 1,2,3-triazoles (**45-59**)

A mixture of *m*-NO_2-aryl-azide **44** (0.6 mmol), the appropriate alkynes (0.9 mmol), copper iodide (I) (0.1 mmol) in 3 mL of acetonitrile was stirred and monitored by silica gel TLC. The solvent was then removed under reduced pressure and the reaction mixture was purified on a silica gel column, using a mixture of hexane/ethyl acetate of increasing polarity.

4-(1-(3-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)aniline (**45**)

The reaction of compound **44** (100 mg, 0.6 mmol) and 4-ethynylaniline (100 mg, 0.9 mmol) yielded product **45**, (137 mg, 0.5 mmol, 80% yield), as an orange solid; mp 210-211 ºC; IR (KBr) ν / cm^{-1} 3450, 3367 (NH), 3102 (CH), 1567, 1522 (C=C), 1346 (N=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (1H, s), 8.74 (1H, s), 8.42 (d, 1H, *J* 8.2 Hz), 8.31 (d, 1H, *J* 8.2 Hz), 7.90 (t, 1H, *J* 8.2 Hz), 7.60 (d, 2H, *J* 8.2 Hz), 6.65 (d, 2H, *J* 8.2 Hz), 5.31 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.1, 148.8, 148.6, 137.4, 131.6, 126.4, 125.5, 122.9, 117.5, 117.3, 114.0, 112.4.; calcd. for ($C_{14}H_{11}N_5O_2$): C, 59.78; H, 3.94; N, 24.90; found: C, 59.56; H, 4.09; N, 24.85.

1-(3-nitrophenyl)-4-(4-nitrophenyl)-1*H*-1,2,3-triazole (**46**)

The reaction of compound **44** (100 mg, 0.6 mmol) and 1-ethynyl-4-nitrobenzene (134 mg, 0.9 mmol) yielded product **46**, (176 mg, 0.57 mmol, 93% yield), as an orange solid; mp 268-270 ºC; IR (KBr) ν / cm^{-1} 3096 (CH), 1603, 1522 (C=C), 1344 (N=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (1H, s), 8.79 (1H, s), 8.46 (d, 1H, *J* 7.8 Hz), 8.38 (3H, m), 8.22 (d, 2H, *J* 9.0 Hz), 7.95 (t, 1H, *J* 8.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.1, 148.8, 148.6, 137.4, 131.6, 126.4, 125.5, 122.9, 117.5, 117.3, 114.0, 112.4.; calcd. for ($C_{14}H_9N_5O_4$): C, 54.02; H, 2.91; N, 22.50; found: C, 54.02; H, 3.33; N, 22.58.

4-(4-Methoxyphenyl)-1-(3-nitrophenyl)-1*H*-1,2,3-triazole (**47**)

The reaction of compound **44** (100 mg, 0.6 mmol) and 1-ethynyl-4-methoxybenzene (121 mg, 0.9 mmol) yielded product **47**, (143 mg, 0.5 mmol, 79% yield), as a yellow solid; mp 210-211 ºC; IR (KBr) ν / cm^{-1} 3096 (CH), 1603, 1522 (C=C), 1344 (N=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (1H, s), 8.76 (1H, s), 8.44 (dd, 1H, *J* 8.4, 1.2 Hz), 8.33 (dd, 1H, *J* 8.0, 1.6 Hz), 7.92 (t, 1H, *J* 8.0 Hz), 7.88 (d, 2H, *J* 8.8 Hz), 7.08 (d, 2H, *J* 8.4 Hz), 3.82 (3H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.4, 148.5, 147.5, 137.2, 131.4, 126.7, 125.7, 122.8, 122.3, 118.8, 114.4, 114.3, 55.1.

2-((1-(3-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl) isoindoline-1,3-dione (**51**)

The reaction of compound **44** (100 mg, 0.6 mmol) and 2-(prop-2-yn-1-yl)isoindoline-1,3-dione (169 mg, 0.9 mmol) yielded product **51**, (198 mg, 0.57 mmol, 93% yield), as a pink solid; mp 208-209 ºC; IR (KBr) ν / cm^{-1} 3138 (CH), 3093 (CH), 1705 (C=O), 1530, (C=C), 1346 (N=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (1H, s), 8.67 (1H, s), 8.36 (dd, 1H, *J* 7.6, 1.2 Hz), 8.29 (dd, 1H, *J* 8.4, 1.6 Hz), 7.93-7.84 (5H, m), 4.96 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 148.3, 143.9, 136.9, 134.3, 131.5, 131.2, 125.8, 123.0, 122.9, 121.6, 114.5, 32.7; calcd. for ($C_{17}H_{11}N_5O_4 \times 0.6\ H_2O$): C, 56.68; H, 3.42; N, 19.45; found: C, 56.25; H, 3.04; N, 19.39.

1-(3-Nitrophenyl)-4-propyl-1*H*-1,2,3-triazole (**52**)

The reaction of compound **44** (100 mg, 0.6 mmol) and pent-1-yne (62 mg, 0.9 mmol) yielded product **52**, (126 mg, 0.54 mmol, 89% yield), as a yellow solid; mp 109-110 ºC; IR (KBr) ν / cm^{-1} 3147, 3098 (CH), 1537, (C=C), 1347 (N=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, s), 8.27 (d, 1H, *J* 7.2 Hz), 8.19 (d, 1H, *J* 8.0 Hz), 7.83 (1H, s), 7.73 (t, 1H, *J* 7.6 Hz), 2.80 (t, 2H, *J* 6.8 Hz), 1.78 (2H, m), 1.03 (t, 3H, *J* 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.2, 148.3, 137.3, 130.2, 125.1, 122.2, 118.0, 114.3, 27.0, 21.9, 13.1; calcd. for ($C_{11}H_{12}N_4O_2$): C, 56.89; H, 5.21; N, 24.12; found: C, 56.69; H, 5.13; N, 23.91.

4-Butyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazole (**53**)

The reaction of compound **44** (100 mg, 0.6 mmol) and hex-1-yne (75 mg, 0.9 mmol) yielded product **53**, (135 mg, 0.55 mmol, 90% yield), as a yellow solid; mp 101-102 ºC; IR (KBr) ν / cm^{-1} 3146 (CH), 3094 (CH), 1533, (C=C), 1346 (N=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, s), 8.27 (d, 1H, *J* 8.0 Hz), 8.19 (d, 1H, *J* 8.0 Hz), 7.83 (1H, s), 7.73 (t, 1H, *J* 8.0 Hz), 2.83 (t, 2H, *J* 8.0 Hz), 1.48-1.38 (2H, m), 0.98-0.93 (2H, m), 1.0 (t, 3H, *J* 8.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150, 148.9, 137.9, 130.8, 125.7, 122.8, 118.5, 114.9, 31.3, 25.3, 22.3, 13.8.

X-ray analysis

X-ray data were collected at 150 K using MoKα (0.71073 A) on an Agilent Gemini diffractometer equipped with a charge-coupled device (CCD) area detector. The CrysAlisPro software package[40] was used for data collection and data reduction. The data were corrected empirically for absorption using spherical harmonics using the SCALE3 ABSPACK[41] scaling algorithm. The structure was solved by direct methods using SHELXS-97[42] and refined by full-matrix least squares on F^2 using SHELXL-97.[43] All non-hydrogen atoms were successfully refined using anisotropic displacement parameters. Hydrogen atoms were found in the Fourier difference synthesis and fixed.

Antimycobacterial activity

Isolates and strain preparation

The antimicrobial activity of the compounds **5**-**15** and **18**-**38** were evaluated against *M. tuberculosis* H_{37}Rv (ATCC 27294) pan-susceptible. The bacterial suspensions were prepared in sterile water containing beads of glass of 3 mm. The suspension was homogenized by vortex agitation and the turbidity was adjusted in agreement with tube one of the scale of McFarland (3.2×106 cfu mL^{-1}). The inoculum was prepared diluting the bacterial suspension in the proportion of 1:20 in medium 7H9 Middlebrook (Difco, Becton-Dickinson) enriched with 10% oleic acid, albumin, dextrose and catalase (OADC-BBL®).

Minimum inhibitory concentration determination

The resazurin microtiter assay (REMA) was performed adapting the technique proposed by Palomino *et al.*[44] Briefly, 200 µL of sterile water was added to all outer-perimeter wells of the sterile 96 well plates to minimize evaporation of the medium in the test wells during incubation. Hereafter, 100 µL of Middlebrook 7H9 broth (Difco Laboratories) enriched with 10% OADC was placed in each tests well of a plate, and a two-fold serial dilution of the compounds (prepared in dimethyl sulfoxide (DMSO)) was made on the plate, with range concentrations from 200 to 6.25 µg mL^{-1}. A volume of 100 µL of the inoculum was added to each well and incubated at 37 °C for seven days. After these, 30 µL of resazurin solution were added to each well and the plate returned to the incubator for two more days. The alteration in the oxidized state (blue color) to reduced state (pink) was scored as bacterial growth. The minimal inhibition concentration (MIC) was defined was defined as the lowest compound concentration that inhibited bacterial growth, which prevented a color change from blue to pink.

Supplementary Information

Supplementary information (^{1}H and ^{13}C NMR spectra for all compounds and ESI-MS for unpublished compounds) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Crystallographic data for the structure were deposited in the Cambridge Crystallographic Data Centre, with number CCDC 976384, 976385 and 974795 for compounds **12**, **19** and **29**, respectively. Copies of the available material can be obtained, free of charge on application to the director, CCDC, 12 Union Road, Cambridge CH21EZ, UK (fax: +44-1223-336-033, e-mail: deposit@ccdc.cam.ac.uk or at http://www.ccdc.cam.ac.uk).

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