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Novel 1,4-Substituted-1,2,3-Triazoles as Antitubercular Agents

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Tuberculosis (TB) remains a pressing unmet medical need, particularly with the emergence of multidrug-resistant and extensively drug-resistant tuberculosis. Here, a series of 1,4-substituted-1,2,3-triazoles have been synthesized and evaluated as potential antitubercular agents. These compounds were assembled via click chemistry in high crude purity and in moderate to high yield. Of the compounds tested, 12 compounds showed promising antitubercular activity with six possessing minimum inhibitory concentration (MIC) values $<10\ \mu g\,mL^{-1}$, and total selectivity for *Mycobacterium tuberculosis* (Mtb) growth inhibition. A second set of 21 compounds bearing variations on ring C were synthesized and evaluated. This second library gave an additional six compounds displaying MIC values $\leq 10\ \mu g\,mL^{-1}$ and total selectivity for Mtb growth inhibition. These compounds serve as an excellent starting point for further development of antitubercular therapies.

Tuberculosis (TB) has plagued humanity for thousands of years and has claimed millions of lives over this time. In 2012, approximately 8.6 million people developed TB and 1.3 million died as a result.[1] TB infection is caused by *Mycobacterium tuberculosis* (Mtb), which predominantly causes disease in the lungs resulting in cough, fever and weight loss. Despite the preventability of this disease, it is still present in first-world countries although more than 95% of all deaths attributed to TB occur in middle-to-low economically developed countries.[2] Individuals with compromised immune systems, such as people who are HIV-positive, are at a great risk of contracting TB. Indeed, over 30% of people with HIV are co-infected with Mtb and are approximately 30 times more likely to develop active TB which, if untreated, is almost always fatal in this population. In addition to this, multidrug-resistant tuberculosis (MDR-TB) is becoming more common, with over 450000 people contracting MDR-TB in 2012, due to the extensive use of isoniazid and rifampicin, and the World Health Organization estimates that approximately 10% of these cases were extensively drug-resistant tuberculosis (XDR-TB). As such, the development of novel molecular scaffolds targeting Mtb is an area of increasingly active investigation globally.

Over the past decade, a range of approaches to the development of antitubercular compounds has been undertaken, though TB remains a challenge to treat due to the extremely thick hydrophobic cell wall of Mtb. A useful review regarding antitubercular drug candidates was published in 2012.[3] One strategy, which is becoming more common is the use of 1,2,3-triazoles incorporated into the molecular scaffold, either as a means to link several molecular portions together or as a key part of the pharmacophore.[4–6] The surge of enthusiasm for the inclusion of this moiety within medicinal scaffolds most likely has arisen from several factors, including: 1) ease of installation via click chemistry; 2) general high yields; 3) amide isosterism; and 4) broad functional group tolerance.[5,7]

Recent work by Boechat et al.[8] and Kantevari et al.[5,6] investigated the use of rapidly accessed 1,2,3-triazoles as novel antitubercular agents (**1** and **2**, respectively; Figure 1). These compounds showed good minimum inhibitory concentration (MIC) values (typically $<10\ \mu g\,mL^{-1}$) against the H37Rv strain of Mtb, and compound **1**[8] also showed a lack of toxicity against a human liver cell line. In a similar approach, Kim and co-workers[9] synthesized a range of 1,2,3-triazole-derived econazole/miconazole derivatives MIC values as low as $8\ \mu g\,mL^{-1}$.

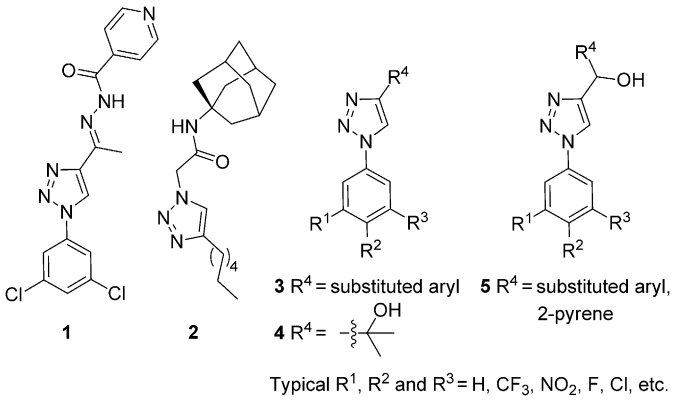

Figure 1. Previously described triazole-containing antitubercular compounds **1** and **2**, and the focus of this study, compounds **3**–**5**.

In this study, we sought to determine whether the 1,2,3-triazole moiety can be used as an *N*-phenylamide isostere in the development of antitubercular agents. Here, we present the

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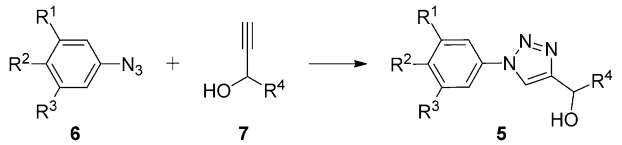
rapid synthesis and evaluation of 1,4-substituted-*N*-aryl-1,2,3-triazoles with substitution variations on the 1-phenyl and triazole-4-position substituents. While the majority of these compounds do not possess potent antitubercular activity, several had promising potency against Mtb H37Rv with MIC values $<10\ \mu g\,mL^{-1}$ and form the basis of future development for more potent compounds.

We recently reported the rapid synthesis and evaluation of novel 1,4-substituted *N*-phenyl-1,2,3-triazoles (general structure **3**; Figure 1) as androgen receptor antagonists.[10] The primary motivation of that work was to use 1,4-substituted triazole as an amide isostere for electron-deficient *N*-phenylamides found in common antiandrogenic compounds. A search of the literature showed that similar *N*-phenylamides have shown antitubercular activity,[11] and based on this, we further explored this premise. The aryl azides for click chemistry were synthesized based on the previously described optimized reaction conditions using typical copper-mediated azide–alkyne cycloaddition (CuAAC).[10] The chosen alkyne reaction partners were propargyl alcohols **8**, which were synthesized in-house via ethynyl Grignard addition to the corresponding aldehyde.

Using copper(II) sulfate/ascorbic acid combination under microwave irradiation to react phenyl azides **7** with propargyl alcohols **8** gave the desired triazoles (**6**) in good to excellent yield. Presumably the lowest yield (49%; Table 1, Entry 4) was due to poor solubility of the propargylic alcohol in the aqueous system. Nevertheless, all compounds were isolated in good crude purity and high enough yield to allow for biological evaluation. Note that despite the high crude purity, all compounds were purified to greater than 95% purity prior to biological evaluation.

Compounds **5a–l** as well as **8a–g**, **9a–g**, **10a** and **10b** (Figure 2), which were on hand from our previously described antiandrogenic study,[10] were submitted for biological evaluation as they are still suitable compounds to investigate under the hypothesis of this study. This gave a total of 33 compounds for preliminary antitubercular evaluation. It was thought that by pooling the compounds together a greater idea of potential favorable/nonfavorable interactions could be gleaned thus informing the development of a second, more focused library of compounds to be examined (see below).

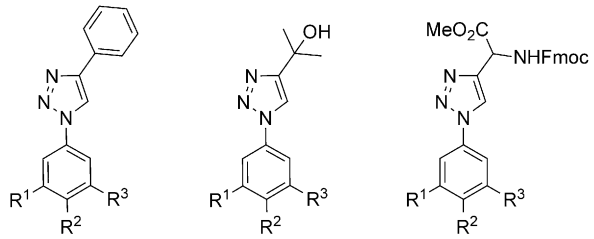
Table 1. Formation of triazoles **5**.[a]



6 **7** **5**

Entry	R^1	R^2	R^3	R^4	Product	Yield [%][b]
1	H	CN	CF_3	H	**5a**	53
2	H	NO_2	CF_3	H	**5b**	68
3	H	CN	CF_3	2-pyrene	**5c**	77
4	H	NO_2	CF_3	2-pyrene	**5d**	49
5	H	CN	CF_3	C_6F_5	**5e**	67
6	H	NO_2	CF_3	C_6F_5	**5f**	69
7	H	CN	CF_3	3,5-BrPh	**5g**	96
8	H	NO_2	CF_3	3,5-BrPh	**5h**	94
9	H	CN	CF_3	4-BrPh	**5i**	89
10	H	NO_2	CF_3	4-BrPh	**5j**	73
11	H	CN	CF_3	4-FPh	**5k**	81
12	H	NO_2	CF_3	4-FPh	**5l**	83

[a] *Reagents and conditions*: $CuSO_4$, ascorbic acid, H_2O, microwave, 100 °C, 30 min. [b] Isolated yield after purification.



8a–g **9a–g** **10a,b**

a	b	c	d	e	f	g
R^1 = H	R^1 = H	R^1 = H	R^1 = H	R^1 = H	R^1 = CF_3	R^1 = H
R^2 = CN	R^2 = NO_2	R^2 = NO_2	R^2 = CN	R^2 = Cl	R^2 = H	R^2 = H
R^3 = CF_3	R^3 = CF_3	R^3 = H	R^3 = H	R^3 = H	R^3 = CF_3	R^3 = H

Figure 2. Previously synthesized triazoles[10a] incorporated into this study.

These compounds were evaluated against a panel of bacteria including Mtb H37Rv (ATCC 27394), *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli* as previously described,[12] using isoniazid as the positive control. Of the compounds tested, 12 showed some degree of antitubercular activity, and six compounds showed full inhibition of growth for Mtb only. Note that in some cases the other bacterial strains in the panel showed slowed growth in the presence of high concentrations of these compounds but not inhibition. The structures of the compounds synthesized in this study (i.e., triazoles of general structure **5**) and their corresponding MIC values are shown in Figure 3, with compounds with substantial potency (MIC $<10\ \mu g\,mL^{-1}$) framed.

Compounds series **5** gave six compounds with some antitubercular activity, two of which, **5d** and **5l**, possessed MIC values $<10\ \mu g\,mL^{-1}$. An interesting trend was observed here, in that the aryl substituent on the alcohol seemed to determine activity, as the aryl triazole portion was consistent—effectively giving three 'sets' of active compounds. Another trend was observed where the compounds bearing a nitro functionality were always observed to be more active that the analogous compound with a cyano group in the 4-position. The degree of improvement was variable between compounds of each set, for example, **5j** is 1.5 times better than **5i**, whereas **5d** is 3.7 times more potent than **5c**. It is perhaps not surprising that the nitro-aromatic compounds are the most potent since Mtb can reductively activate such molecules.[12,13]

Of the compounds from series **8** and **9**, five were active (Figure 4). In direct contradiction to the previous set of compounds (Figure 3), only one nitro-aromatic compound (**8b**) was active against Mtb, and it was the weakest of this series by far. Intriguingly, the most potent compounds were structurally very simple, such as **8g**, **8f**, and **8e**, possessing MIC values of 2.1, 3.4, and 9.6 $\mu g\,mL^{-1}$, respectively. The contrast in struc-

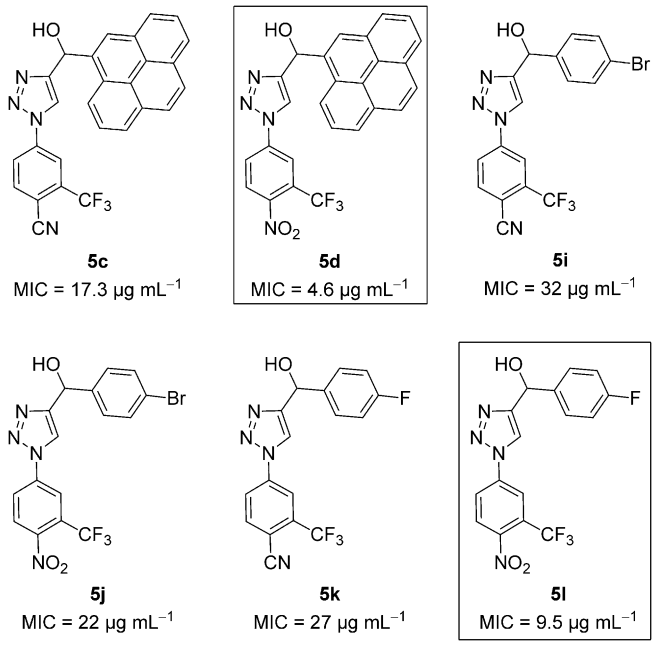


Figure 3. Compounds displaying antitubercular activity from series **5**. Framed compounds exhibit substantial potency (MIC $< 10\ \mu g\,mL^{-1}$).

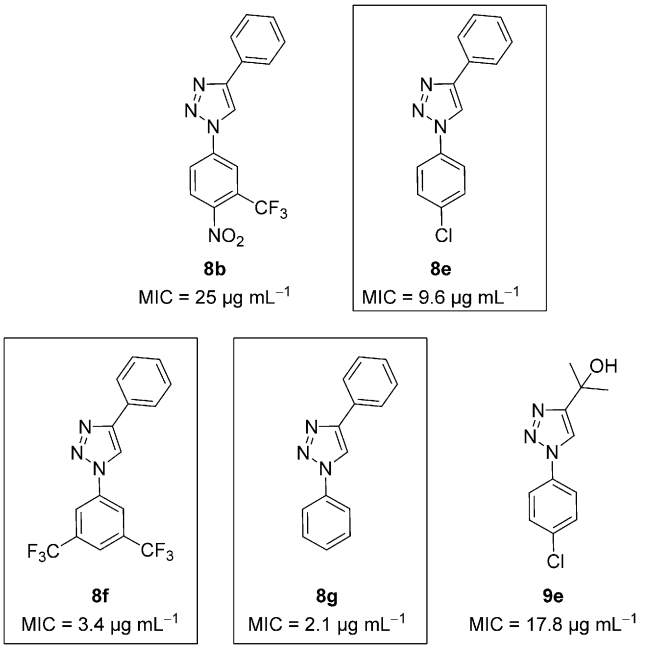


Figure 4. Compounds displaying antitubercular activity from series **8** and **9**. Framed compounds exhibit substantial potency (MIC $< 10\ \mu g\,mL^{-1}$).

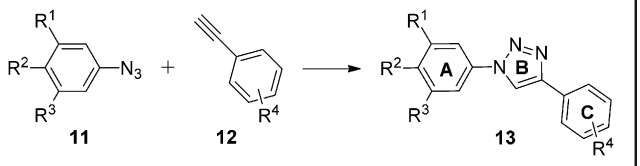
turally active compounds between those in Figure 3 and Figure 4 suggest a different mode of action.

The nitroaromatic compounds have generally been associated with a very high frequency of mutation in Mtb due to the ease of inactivation of the various processes required for nitro reduction[12] making compounds **8g**, **8f**, and **8e** particularly attractive for follow-up since these are unlikely prodrugs and might inhibit a specific target.

From this preliminary study, it was seen that compounds consisting of three aromatic rings (e.g., **8a**–**g**) were the better class of potential antitubercular compounds. Additionally, compounds containing an *N*-aryl triazole moiety bearing either a 4-nitro-3-trifluoromethyl, 3,5-trifluoromethyl, or phenyl group showed the most promise. Therefore, considering that **8b**, **8f**, and **8g** all have unsubstituted aryl ring substituents on ring C (see **13**, below), our next objective was to vary this moiety. In doing this, we chose the most promising azide units that correspond to **8b**,**f**,**g** cross-sectioned with a range of phenyl acetylenes that possess various substitution on ring C.

The synthesis of these compounds proceeded smoothly and in poor to good yield (20–70%; Table 2). Anilinic triazoles **13d**, **13h**, and **13l** represent an interesting opportunity to derivatize these compounds by acylation of the aniline to give various amides. Amide formation proceeded in high yield under mild conditions for all compounds **14a**–**i** (Table 3). We chose a simple acetate amide as we thought this unit imparts amide character without additional lipophilicity. Whereas, the octanoyl amide was chosen to impart lipophilicity, as it was thought that this might assist the passage of these compounds through the thick Mtb cell wall, and finally a simple benzoyl amide was chosen.

Table 2. Second library of compounds **13** bearing aryl substitution.[a]

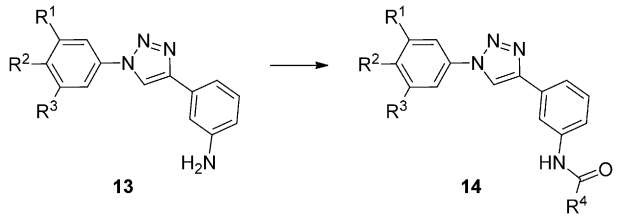


Entry	R^1	R^2	R^3	R^4	Product	Yield [%][b]
1	H	H	H	2-F	**13a**	20
2	H	H	H	4-Cl	**13b**	40
3	H	H	H	4-OEt	**13c**	55
4	H	H	H	3-NH_2	**13d**	50
5	CF_3	H	CF_3	2-F	**13e**	63
6	CF_3	H	CF_3	4-Cl	**13f**	64
7	CF_3	H	CF_3	4-OEt	**13g**	52
8	CF_3	H	CF_3	3-NH_2	**13h**	54
9	H	NO_2	CF_3	2-F	**13i**	70
10	H	NO_2	CF_3	4-Cl	**13j**	40
11	H	NO_2	CF_3	4-OEt	**13k**	67
12	H	NO_2	CF_3	3-NH_2	**13l**	64

[a] *Reagents and conditions*: $CuSO_4$, ascorbic acid, H_2O, microwave, 100 °C, 30 min. [b] Isolated yield after purification.

With compounds **13a**–**l** and **14a**–**i** in hand, our attention focused on evaluation of these compounds for their antitubercular activity, in addition to selectivity against a representative panel of other bacteria (*S. aureus*, *B. subtilis*, *P. aeruginosa,* and *E. coli)*. These compounds showed complete selectivity towards Mtb compared with the other bacterial strains investigated (Table 4). The structural elaborations of *N*-phenyl triazoles (**13a**–**d**) showed that all modifications made to the parent scaffold resulted in a decrease in MIC value relative to the parent compound (**8g**). This was consistent with the observed

Table 3. Formation of amides **14**.



Entry	Starting material	R^1	R^2	R^3	R^4	Product	Yield [%][b]
1	**13d**	H	H	H	CH_3	**14a**	86
2	**13d**	H	H	H	$(CH_2)_6CH_3$	**14b**	75
3	**13d**	H	H	H	Ph	**14c**	77
4	**13h**	CF_3	H	CF_3	CH_3	**14d**	85
5	**13h**	CF_3	H	CF_3	$(CH_2)_6CH_3$	**14e**	91
6	**13h**	CF_3	H	CF_3	Ph	**14f**	89
7	**13l**	H	NO_2	CF_3	CH_3	**14g**	78
8	**13l**	H	NO_2	CF_3	$(CH_2)_6CH_3$	**14h**	45
9	**13l**	H	NO_2	CF_3	Ph	**14i**	77

[a] *Reagents and conditions*: R^4COCl, Et_3N (3 equiv), CH_2Cl_2, 16 h, RT. [b] Isolated yield after purification.

Table 4. Minimum inhibitory concentration (MIC) values for **13a–l** and **14a–i** against *Mycobacterium tuberculosis* (Mtb) H37Rv.[a]

Compd	MIC [$\mu g\,mL^{-1}$]	Compd	MIC [$\mu g\,mL^{-1}$]
13a	5 ± 2	**14a**	10 ± 5
13b	7 ± 3	**14b**	26 ± 13
13c	>100	**14c**	28 ± 14
13d	9 ± 4	**14d**	>100
13e	>100	**14e**	>100
13f	5 ± 2	**14f**	>100
13g	15 ± 7	**14g**	>100
13h	>100	**14h**	>100
13i	13 ± 6	**14i**	>100
13j	7 ± 3		
13k	8 ± 4		
13l	13 ± 6	Isoniazid	0.02 ± 0.01

[a] Data represent the mean $\pm$SD of two independent experiments performed in duplicate.

activities for **13e–h**, whereby all modifications made to parent scaffold **8f** resulted in a small increase in MIC value. Interestingly, 2-fluoro (**13e**) and anilinic (**13h**) substitution were not tolerated at all, with no bactericidal properties observed for either compound. We were pleased to observe that all modifications made to parent scaffold **8b** resulted in compounds with improved MIC values. Indeed, **13j** and **13k** possess Mtb toxicity threefold more potent than the parent. To our surprise, the addition of amide groups to the phenyl ring of triazoles **13d**, **13h**, and **13l** resulted in compounds with vastly decreased MIC values or total abolition of antimicrobial properties. The reason for this is unknown and will be the subject of ongoing studies.

In conclusion, we have synthesized a series of compounds bearing 1,4-substituted triazoles and have evaluated them for their antitubercular activity. These compounds were rapidly accessed via a simple two-step synthetic sequence, which is very amenable to library generation. From the initial 35 compounds evaluated in this study, 12 possess some antitubercular activity with half of these displaying MIC values $<10\,\mu g\,mL^{-1}$ and selectivity of Mtb across a panel of gram-positive and negative bacteria. We then synthesized a second library of 21 compounds, which possess structural variation on ring C of the triazole. These analogues demonstrate that an amide unit on ring C is not well tolerated. Nevertheless, we have shown that this simple tri-aromatic molecular scaffold is an excellent starting point for the development of more potent antitubercular agents and mode of action studies.

Experimental Section

General procedures for CuAAC reaction: Alkyne (1 mmol), azide (1 mmol), $CuSO_4$ (10 mol%) and ascorbic acid (20 mol%) were stirred in water (3 mL) under microwave irradiation at 100°C for 30 min. The solution was cooled to RT and then diluted with CH_2Cl_2 (3 mL) and stirred for 3 min. The product was then extracted using CH_2Cl_2 (2×10 mL), and the organic layer washed with water (10 mL), 4 M aq HCl (5 mL) and water (5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the desired product, which was purified by dissolving the crude product in the minimal amount CH_3Cl (2 mL) and then adding cold petroleum spirits (15 mL) to cause precipitation followed by collection by vacuum filtration to isolate the solid product in >95% purity (determined by ^1H NMR).

General procedure for the synthesis of propargylic alcohols 7: Ethynyl Grignard (3 mmol) was added to a solution of aldehyde (1 mmol) in THF at 0°C. The solution was stirred overnight and allowed to come to RT. The reaction was quenched with 1 M aq HCl, and the crude material extracted with EtOAc (3×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the desired product, which was purified by flash chromatography to give the title alcohol.

General procedure for the synthesis of amides 14a–i: Anilinic triazole (1 equiv) and Et_3N (3 equiv) were dissolved in CH_2Cl_2 (5 mL mmol^{-1}), and the appropriate acid chloride (2.0 equiv) was added. The solution was stirred overnight at RT. The reaction was quenched by addition of 1 M aq HCl (10 mL), and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (20 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was redissolved in $CHCl_3$ (1 mL/100 mg) and then precipitated by the addition of RT petroleum spirits (30 mL). The resultant precipitate was isolated by vacuum filtration to give the product as a powder in >95% purity (determined by ^1H NMR).

For characterization data and accompanying spectra, see the Supporting Information.

Antimicrobial susceptibility assays: MIC assays against Mtb H37Rv were set up as previously described.[14] By visual inspection, all compounds were soluble at 100 μM in 0.5% DMSO/water (for details, see the Supporting Information). MIC determinations for *Staphylococcus aureus* ATCC 13801, *Bacillus subtilis*, *Pseudomonas aeruginosa* PA01, and *Escherichia coli* HB101 were similarly set up using Luria–Bertani broth with growth evaluated after overnight incubation at 37°C.[14] In all cases, evaluation was measured in duplicate from two independent experiments. Note that it is not unusual to observe a 100% variation in MIC value.[15]

Acknowledgements

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Keywords: antibacterial agents · azides · click chemistry · *Mycobacterium tuberculosis* · triazoles · tuberculosis

[1] I. Hershkovitz, H. D. Donoghue, D. E. Minnikin, G. S. Besra, O. Y. C. Lee, A. M. Gernaey, E. Galili, V. Eshed, C. L. Greenblatt, E. Lemma, G. K. Bar-Gal, M. Spigelman, *PLoS ONE* **2008**, *3*, e3426.

[2] Global Tuberculosis Report **2013**, World Health Organization (Geneva, Switzerland), ISBN: 978-92-4-156465-6.

[3] B. Villemagne, C. Crauste, M. Flipo, A. R. Baulard, B. Déprez, N. Willand, *Eur. J. Med. Chem.* **2012**, *51*, 1 – 16.

[4] a) M. S. Costa, N. Boechat, E. A. Rangel, C. da Silva Fde, A. M. de Souza, C. R. Rodrigues, H. C. Castro, I. N. Junior, M. C. Lourenco, S. M. Wardell, V. F. Ferreira, *Bioorg. Med. Chem.* **2006**, *14*, 8644 – 8653; b) P. P. Jain, M. S. Degani, A. Raju, M. Ray, M. G. Rajan, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6097 – 6105; c) R. R. Kondreddi, J. Jiricek, S. P. Rao, S. B. Lakshminarayana, L. R. Camacho, R. Rao, M. Herve, P. Bifani, N. L. Ma, K. Kuhen, A. Goh, A. K. Chatterjee, T. Dick, T. T. Diagana, U. H. Manjunatha, P. W. Smith, *J. Med. Chem.* **2013**, *56*, 8849 – 8859; d) G. R. Labadie, A. de La Iglesia, H. R. Morbidoni, *Mol. Diversity* **2011**, *15*, 1017 – 1024; e) C. Menendez, A. Chollet, F. Rodriguez, C. Inard, M. R. Pasca, C. Lherbet, M. Baltas, *Eur. J. Med. Chem.* **2012**, *52*, 275 – 283; f) C. Menendez, S. Gau, C. Lherbet, F. Rodriguez, C. Inard, M. R. Pasca, M. Baltas, *Eur. J. Med. Chem.* **2011**, *46*, 5524 – 5531; g) C. Menendez, F. Rodriguez, A. L. Ribeiro, F. Zara, C. Frongia, V. Lobjois, N. Saffon, M. R. Pasca, C. Lherbet, M. Baltas, *Eur. J. Med. Chem.* **2013**, *69*, 167 – 173; h) F. Mir, S. Shafi, M. S. Zaman, N. P. Kalia, V. S. Rajput, C. Mulakayala, N. Mulakayala, I. A. Khan, M. S. Alam, *Eur. J. Med. Chem.* **2014**, *76*, 274 – 283; i) M. Muthukrishnan, M. Mujahid, P. Yogeeswari, D. Sriram, *Tetrahedron Lett.* **2011**, *52*, 2387 – 2389; j) G. S. Timmins, S. Master, F. Rusnak, V. Deretic, *Antimicrob. Agents Chemother.* **2004**, *48*, 3006 – 3009; k) A. T. Tran, K. M. Cergol, W. J. Britton, S. A. Imran Bokhari, M. Ibrahim, A. J. Lapthorn, R. J. Payne, *Med. Chem. Commun.* **2010**, *1*, 271 – 275.

[5] D. Addla, A. Jallapally, D. Gurram, P. Yogeeswari, D. Sriram, S. Kantevari, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1974 – 1979.

[6] a) S. R. Patpi, L. Pulipati, P. Yogeeswari, D. Sriram, N. Jain, B. Sridhar, R. Murthy, T. Anjana Devi, S. V. Kalivendi, S. Kantevari, *J. Med. Chem.* **2012**, *55*, 3911 – 3922; b) T. Yempala, J. P. Sridevi, P. Yogeeswari, D. Sriram, S. Kantevari, *Eur. J. Med. Chem.* **2014**, *71*, 160 – 167.

[7] a) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128 – 1137; b) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210 – 216; c) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905 – 4979.

[8] N. Boechat, V. F. Ferreira, S. B. Ferreira, M. de Lourdes G. Ferreira, F. de C. da Silva, M. M. Bastos, M. dos S. Costa, M. C. S. Lourenco, A. C. Pinto, A. U. Krettli, A. C. Aguiar, B. M. Teixeira, N. V. da Silva, P. R. C. Martins, F. A. F. M. Bezerra, A. L. S. Camilo, G. P. da Silva, C. C. P. Costa, *J. Med. Chem.* **2011**, *54*, 5988 – 5999.

[9] S. Kim, S. N. Cho, T. Oh, P. Kim, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6844 – 6847.

[10] a) J. M. Altimari, B. Niranjan, G. P. Risbridger, S. S. Schweiker, A. E. Lohning, L. C. Henderson, *Bioorg. Med. Chem.* **2014**, *22*, 2692 – 2706; b) J. M. Altimari, B. Niranjan, G. P. Risbridger, S. S. Schweiker, A. E. Lohning, L. C. Henderson, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4948 – 4953.

[11] a) I.-Y. Lee, T. D. Gruber, A. Samuels, M. Yun, B. Nam, M. Kang, K. Crowley, B. Winterroth, H. I. Boshoff, C. E. Barry III, *Bioorg. Med. Chem.* **2013**, *21*, 114 – 126; b) K. A. Rawls, P. T. Lang, J. Takeuchi, S. Imamura, T. D. Baguley, C. Grundner, T. Alber, J. A. Ellman, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6851 – 6854.

[12] T. Mukherjee, H. Boshoff, *Future Med. Chem.* **2011**, *3*, 1427 – 1454.

[13] N. R. Tawari, M. S. Degani, *J. Comput. Chem.* **2010**, *31*, 739 – 751.

[14] Z. Meissner, H. I. Boshoff, M. Vasan, D. P. Duckworth, C. E. Barry III, C. C. Aldrich, *Bioorg. Med. Chem.* **2013**, *21*, 6385 – 6397.

[15] I. Keren, Y. Wu, J. Inocencio, L. R. Mulcahy, K. Lewis, *Science* **2013**, *339*, 1213 – 1216.

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