Anti-tubercular agents. Part 8: Synthesis, antibacterial and antitubercular activity of 5-nitrofuran based 1,2,3-triazoles

ARTICLE *in* BIOORGANIC & MEDICINAL CHEMISTRY LETTERS · OCTOBER 2013

Impact Factor: 2.42 · DOI: 10.1016/j.bmcl.2013.10.010 · Source: PubMed

Bioorganic & Medicinal Chemistry Letters 23 (2013) 6842–6846

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Anti-tubercular agents. Part 8: Synthesis, antibacterial and antitubercular activity of 5-nitrofuran based 1,2,3-triazoles

Ahmed Kamal [a,*], Syed Mohammed Ali Hussaini [a], Shaikh Faazil [a], Y. Poornachandra [a], G. Narender Reddy [a], C. Ganesh Kumar [a], Vikrant Singh Rajput [b], Chitra Rani [b], Rashmi Sharma [b], Inshad Ali Khan [b], N. Jagadeesh Babu [c]

[a] Medicinal Chemistry and Pharmacology, CSIR-Indian Institute of Chemical Technology, Uppal Road, Hyderabad 500007, India
[b] Clinical Microbiology Division, CSIR-Indian Institute of Integrative Medicine, Jammu 180001, India
[c] Division of X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Uppal Road, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 27 June 2013
Revised 18 September 2013
Accepted 4 October 2013
Available online 11 October 2013

Keywords:
Antimicrobial
Antitubercular
Nitrofuran
Triazole
Biofilm
MRSA

ABSTRACT

A series of 5-nitrofuran–triazole conjugates were synthesized and evaluated for their antimicrobial activity against both Gram-positive and Gram-negative bacterial strains. All the compounds exhibited promising inhibition towards Gram-positive pathogenic strains, while mild inhibitory effects were observed towards Gram-negative bacterial strains. Some of the compounds **8a**, **8b**, **8e**, **8f**, **8h** are most active among the series exhibiting MIC value of 1.17 μg/ml against different bacterial strains. The bactericidal activity is found to be in accordance with the bacterial growth inhibition data. Compound **8e** was found to be equipotent to the standard drug Ciprofloxacin displaying MBC value of 1.17 μg/ml against the bacterial strain *Bacillus subtilis*. The compounds have also demonstrated promising antibacterial activity against the resistant strain MRSA and were found to be effective inhibitors of biofilm formation. The compound **8b** exhibited excellent anti-biofilm activity with IC_{50} value as low as 0.8 μg/ml. These conjugates were also screened for antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ strain. Compound **8e** showed promising antitubercular activity with MIC value of 0.25 μg/ml. Most of these compounds are less toxic to normal mammalian cells than the widely used antibacterial drug Ciprofloxacin.

Infectious diseases caused by microorganisms are a major concern for human survival accounting for almost 50,000 deaths worldwide daily.[1] The development of resistance towards a number of antibiotics contribute a lot to the challenges occurring in the discovery of new therapies.[2] Among the numerous multi-drug resistant Gram-positive bacterial pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA) is a significantly increasing threat to human health.[3] One of the main reason for the growing resistance in bacteria is their ability to develop biofilm. This biomolecular extracellular matrix encapsulating the surface-adhered bacterial communities bestows them 1000 times more resistance to antibiotics than their planktonic counterparts.[4] Medically relevant pathogens grown over biofilms are involved in more than 80% of all bacterial infections[5] and the lack of development of new drug-like molecules to inhibit their formation worsens the problem.

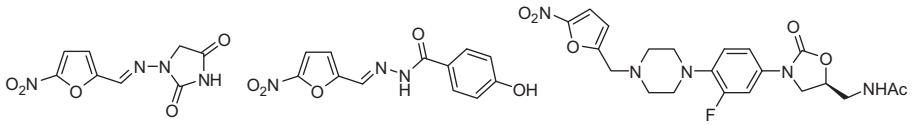
Another pathogen which is a huge menace to the human race is *Mycobacterium tuberculosis*. *Mycobacterium tuberculosis* is an acid-fast Gram-positive bacterium that causes tuberculosis (TB) which is declared as global emergency by WHO due to its latent haven in about one third of the global population.[6,7] Despite the availability of many drugs including vaccines like Bovine Calmette-Guerin (BCG) in the market TB continues to be the leading bacterial infection.[8] This is attributed to emergence of drug resistance occurring due to inappropriate use of antibiotics. Multidrug resistant (MDR)[9] and extensively drug resistant (XDR)[10] TB strains are a big matter of concern for human society. The solution for growing emergence of resistance in the pathogens is the development of new affordable drugs with high potency and low toxicity.

The antimicrobial potential of furan derivatives is well documented.[11] Nitrofurantoin[12] (**1**), nifuroxazide[12] (**2**) and RBX7644[13] (**3**) are few hits from the series of compounds containing nitrofuran moiety (Fig. 1). According to previous reports metabolic reduction of nitro heterocycles (**1** and **2**) by a class of enzymes nitroreductases is responsible for their antimicrobial activity.[14]

In the recent years, triazole nucleus is explored due to its wide biological significance that includes antibacterial,[15] anticancer,[16] antifungal,[17] antiviral,[18] anti-inflammatory[19] and antitubercular[20] properties. Tazobactam[21] (**4**), cefatrizine[22] (**5**) and carboxyamidotriazole[23] (**6**) are the drugs available in the market containing 1,2,3-triazole system (Fig. 2). Further there is an ample evidence in the literature for anti-biofilm activity of 1,2,3-triazole derivatives.[24,25] In continuation to our research to find potent

* Corresponding author. Tel.: +91 40 27193157; fax: +91 40 27193189.
E-mail address: ahmedkamal@iict.res.in (A. Kamal).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.10.010



(1) (2) (3)

Figure 1. Structures of some antimicrobial agents containing nitrofuran moiety.

antimicrobial agents[26–29] and prompted by the diverse biological profile of 1,2,3-triazole as well as nitrofuran heterocycle, we report herein the design and synthesis of nitrofuramide linked triazole hybrids, and evaluation for their anti-mycobacterial as well as antibacterial activities.

The synthetic route to achieve the title compounds **8a–j** is outlined in Scheme 1. As shown, 5-nitro-2-furoic acid was reacted with propargyl amine in presence of EDC and HOBt in CH_2Cl_2. The resultant amide (**7**) containing terminal alkyne functionality was reacted with substituted benzyl azides **11a–j** following click chemistry protocol[30] to obtain the final compounds **8a–j** in good yields (79–92%). The structure of the triazole was initially confirmed by NMR data and was supported by X-ray crystallographic study performed on **8d** to precisely determine the formation of 1,4-isomer. The X-ray results[31] shown in Figure 3 proved the exclusive formation of the 1,4-isomer through the application of copper catalyzed azide alkyne cycloaddition.

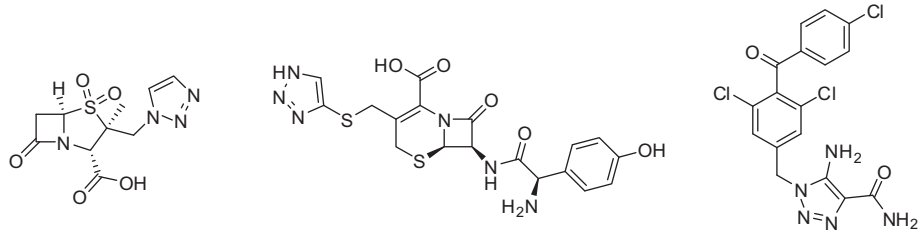
Substituted benzyl azides required as precursors were prepared using a reported procedure[32] as shown in Scheme 2. The corresponding starting benzaldehydes were reduced to respective benzyl alcohol **9a–j** using sodium borohydride in methanol. The respective alcohol obtained was brominated using PBr_3 in dry ether at 0 °C. Overnight stirring of respective benzyl bromide **10a–j** with sodium azide in DMSO afforded the azide intermediates **11a–j** in good yields.

The newly synthesized nitrofuran–triazole derivatives (**8a–j**) were tested for antimicrobial activity against both Gram-positive and Gram-negative bacterial strains. The results (Tables 1 and 2) illustrate that all the ten compounds show different level of inhibitory and bactericidal effects with Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) values ranging from 1.17 to 75 μg/ml. Interestingly, these compounds showed selectivity towards Gram-positive pathogenic strains like *Micrococcus luteus, Staphylococcus aureus* (MLS-16) *and Bacillus subtilis* with MIC and MBC values of <10 μg/ml except for the compound **8j** (MBC value of 18.75 μg/ml against *S. aureus* and *B. subtilis*). Compounds **8b**, **8d**, **8e** and **8j** displayed broad spectrum of activity exhibiting excellent inhibitory as well as bactericidal effects in Gram-positive bacterial strains and moderate activity against Gram-negative bacterial strains. Compounds **8a**, **8h** showed excellent inhibitory activity (1.17 μg/ml) against *M. luteus* MTCC 2470, compound **8b** against *S. aureus* MLS-16 MTCC 2940 and compounds **8e**, **8f** against *B. subtilis* MTCC 121. The bactericidal activity was found to follow the similar trend as that of the inhibitory activity against the respective bacterial strains. The compounds **8a**, **8e**, **8f**, **8g** have demonstrated good bactericidal activity (2.34 μg/ml) against *M. luteus* MTCC 2470, compounds **8b**, **8e**, **8f** against *S. aureus* MLS-16 MTCC 2940 and compound **8d** against *B. subtilis* MTCC 121. Compounds **8e** and **8h** have exhibited excellent bactericidal effects with MBC value of 1.17 μg/ml against *B. subtilis* MTCC 121 and *M. luteus* MTCC 2470, respectively. It is remarkable that compound **8e** was found to be equipotent to the standard drug Ciprofloxacin in terms of bactericidal activity against the bacterial strain *B. subtilis* MTCC 121. However, it was observed that not even a single compound was active against the Gram-negative bacterial strain, *Pseudomonas aeruginosa* MTCC 2453 and the fungal strain, *Candida albicans*, even at the maximum concentration used (150 μg/ml).

The structure–activity relationship study reveals that the substituents with electron withdrawing nature like nitro, fluoro, chloro, trifluoromethyl improved the activity. The compound with nitro group at *meta* position possesses slightly better activity as compared to its *para* counterpart. Substituents fluoro, trifluoromethyl and hydroxyl at *para* position conferred better activity while the methoxy substituent did not have any significant effect on the activity.

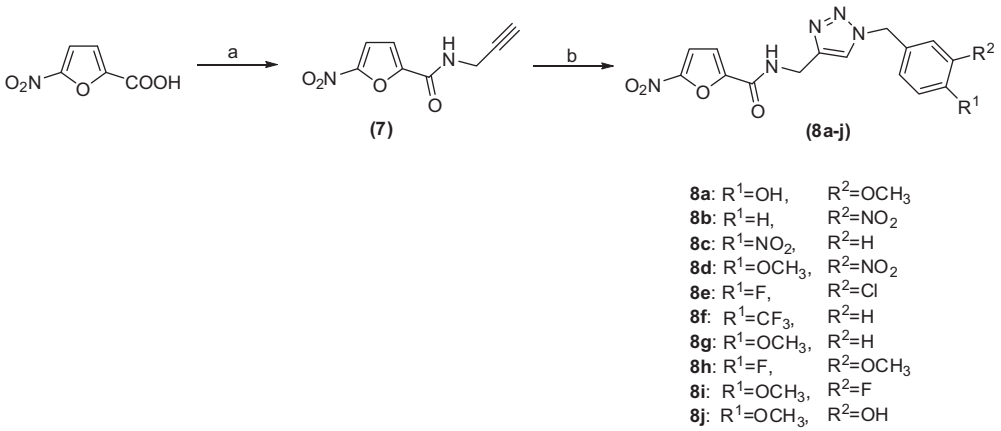
Further these triazole conjugates **8a–e** were tested on two resistant bacterial strains namely methicillin resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococcus* (VRE) and the results are listed in Table 3. The compounds have shown promising antimicrobial activity against MRSA strain whereas against VRE these compounds were found to be inactive. Interestingly the compounds **8b**, **8c**, **8d**, **8e** have shown equal potency to that of Linezolid against MRSA strain with MIC value of 8 μg/ml, while **8a** was moderately active.

These conjugates were also evaluated for anti-biofilm activity against three bacterial strains, namely *Staphylococcus aureus* MTCC 96, *Staphylococcus aureus* MLS-16 MTCC 2940 and *Klebsiella planticola* MTCC 530. The results tabulated in Table 4 show that all the compounds exhibited excellent biofilm inhibition against the strain *S. aureus* MLS-16 MTCC 2940 (IC_{50} <10 μg/ml) and good to moderate activity against other two strains. Complying with the antimicrobial activity, compound **8b** displayed significant anti-biofilm activity among the series against *S. aureus* MLS-16 MTCC 2940



(4) (5) (6)

Figure 2. Structures of some drugs containing triazole nucleus.



Scheme 1. Synthesis of nitrofuran–triazole conjugates. Reagents and conditions: (a) propargyl amine, EDC, HOBt, CH_2Cl_2, rt, 8 h; (b) **11a–j**, $CuSO_4{\cdot}5H_2O$, sodium ascorbate, *t*BuOH/H_2O (1:2), rt, 8 h.

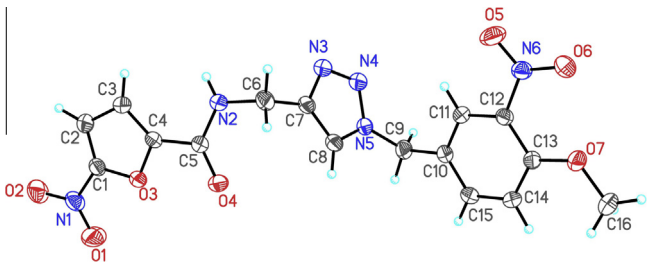
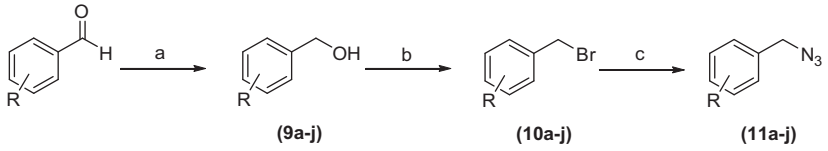


Figure 3. The molecular structure of **8d**, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius.

(0.8 μg/ml). However compound **8e** demonstrated consistent biofilm inhibition with excellent to good activity against *S. aureus* MLS-16 MTCC 2940 (1.1 μg/ml) and other two strains. It is noteworthy that the anti-biofilm activity of all the compounds to a maximum extent is in accordance with antimicrobial activity against the respective strain.

Moreover, the compounds were evaluated for anti-tubercular activity and the results to this regard are tabulated in Table 5. Five of the ten compounds **8a–e** were found to be active on *Mycobacterium tuberculosis* strain $H_{37}Rv$ of which compound **8e** exhibited excellent activity with MIC value of 0.25 μg/ml. The activity of **8e** is four times more than the standard anti-tubercular drug linezolid, whereas other four compounds displayed moderate activity.



Scheme 2. Synthesis of azide precursors. Reagents and conditions: (a) $NaBH_4$, methanol, rt, 2 h; (b) PBr_3, ether, 0 °C, 0.5 h; (c) NaN_3, DMSO, rt, 12 h.

Table 1
MIC values of the compounds **8a–j** against several standard strains

Entry	Compound	Minimum inhibitory concentration (μg/ml)							*C.a*[h]
		M.l[a]	*S.a*[b]	*S.a*[c]	*B.s*[d]	*E.c*[e]	*P.a*[f]	*K.p*[g]	
1	**8a**	1.17	18.75	2.34	4.68	37.5	>150	75.0	—[i]
2	**8b**	4.68	>150	1.17	2.34	9.37	>150	18.75	—[i]
3	**8c**	4.68	>150	4.68	2.34	>150	>150	18.75	—[i]
4	**8d**	4.68	>150	4.68	2.34	18.75	>150	9.37	—[i]
5	**8e**	2.34	18.75	2.34	1.17	18.75	>150	18.75	—[i]
6	**8f**	2.34	>150	2.34	1.17	>150	>150	>150	—[i]
7	**8g**	2.34	37.50	9.37	2.34	75.0	>150	37.50	—[i]
8	**8h**	1.17	>150	9.37	2.34	>150	>150	37.50	—[i]
9	**8i**	4.68	>150	4.68	2.34	>150	>150	18.75	—[i]
10	**8j**	9.37	37.50	9.37	9.37	37.50	>150	18.75	—[i]
Miconazole		—[i]	—[i]	—[i]	—[i]	—[i]	—[i]	—[i]	9.37
Ciprofloxacin		0.58	0.58	0.58	0.58	0.58	0.58	0.58	—[i]

[a] *Micrococcus luteus* MTCC 2470.
[b] *Staphylococcus aureus* MTCC 96.
[c] *Staphylococcus aureus* MLS-16 MTCC 2940.
[d] *Bacillus subtilis* MTCC 121.
[e] *Escherichia coli* MTCC 739.
[f] *Pseudomonas aeruginosa* MTCC 2453.
[g] *Klebsiella planticola* MTCC 530.
[h] *Candida albicans* MTCC 3017.
[i] Not determined.

Table 2
MBC values of the compounds **8a–j** against several standard strains

Entry	Compound	Minimum bactericidal concentration (μg/ml)						
		M.l[a]	*S.a*[b]	*S.a*[c]	*B.s*[d]	*E.c*[e]	*P.a*[f]	*K.p*[g]
1	**8a**	2.34	18.75	4.68	9.37	75.0	>150	75.0
2	**8b**	9.37	>150	2.34	4.68	18.75	>150	37.5
3	**8c**	9.37	>150	4.68	4.68	>150	>150	37.5
4	**8d**	9.37	>150	4.68	2.34	18.75	>150	18.75
5	**8e**	2.34	18.75	2.34	1.17	18.75	>150	37.5
6	**8f**	2.34	>150	2.34	4.68	>150	>150	>150
7	**8g**	2.34	75.0	9.37	4.68	75.0	>150	37.50
8	**8h**	1.17	>150	9.37	4.68	>150	>150	37.50
9	**8i**	9.37	>150	9.37	4.68	>150	>150	18.75
10	**8j**	9.37	75.0	18.75	18.75	75.0	>150	18.75
Ciprofloxacin (Standard)		0.58	0.58	1.17	1.17	0.58	0.58	1.17

[a] *Micrococcus luteus* MTCC 2470.
[b] *Staphylococcus aureus* MTCC 96.
[c] *Staphylococcus aureus* MLS-16 MTCC 2940.
[d] *Bacillus subtilis* MTCC 121.
[e] *Escherichia coli* MTCC 739.
[f] *Pseudomonas aeruginosa* MTCC 2453.
[g] *Klebsiella planticola* MTCC 530.

Table 3
Antimicrobial activity of compounds **8a–e** against resistant bacterial strains

Entry	Compound	R^1	R^2	MIC (μg/ml)	
				MRSA	VRE
1	**8a**	OH	OCH_3	16	>64
2	**8b**	H	NO_2	8	>64
3	**8c**	NO_2	H	8	>64
4	**8d**	OCH_3	NO_2	8	>64
5	**8e**	F	Cl	8	>64
6	**8f**	CF_3	H	NT	NT
7	**8g**	OCH_3	H	NT	NT
8	**8h**	F	OCH_3	NT	NT
9	**8i**	OCH_3	F	NT	NT
10	**8j**	OCH_3	OH	NT	NT
	Linezolid			8	8

NT—Not tested.
MRSA—Methicillin resistant *Staphylococcus aureus*.
VRE—Vancomycin resistant *Enterococcus*.

Table 4
Anti-biofilm activity of compounds **8a–j** against three different bacterial strains

Entry	Compound	IC_{50} values (in μg/ml)		
		Staphylococcus aureus MTCC 96	*Staphylococcus aureus* MLS-16 MTCC 2940	*Klebsiella planticola* MTCC 530
1	**8a**	10.8 ± 0.41	1.7 ± 0.53	42.5 ± 0.21
2	**8b**	84.5 ± 0.23	0.8 ± 0.61	14.5 ± 0.21
3	**8c**	—[a]	3.8 ± 0.11	17.9 ± 0.33
4	**8d**	91.2 ± 0.81	4.1 ± 0.25	6.1 ± 0.54
5	**8e**	13.6 ± 0.79	1.1 ± 0.21	12.2 ± 0.09
6	**8f**	64.7 ± 0.09	8.4 ± 0.81	—[a]
7	**8g**	12.6 ± 0.85	6.1 ± 0.84	24.0 ± 0.17
8	**8h**	—[a]	2.7 ± 0.91	22.7 ± 0.51
9	**8i**	—[a]	3.4 ± 0.41	9.8 ± 0.34
10	**8j**	10.3 ± 0.44	5.1 ± 0.21	11.3 ± 0.17
Erythromycin (Standard)		0.25 ± 0.34	0.21 ± 0.42	0.19 ± 0.19

[a] Not active.

In order to determine the therapeutic potential of the conjugates **8a–j**, these conjugates were tested for their cytotoxicity against two mammalian cell lines, namely MRC-5 (normal lung cell line) and VERO (normal monkey kidney cell line). The results tabulated in Table 6 illustrate that majority of the compounds are less cytotoxic than the standard drug Ciprofloxacin. Particularly the compounds **8f**, **8i** and **8b**, **8e** were found to exhibit approximately 50% less cytotoxic effects than Ciprofloxacin against MRC-5 and VERO cell lines, respectively. On an overall basis compounds **8e**, **8f** and **8i** exhibited lowest cytotoxic effects among the series.

The antibacterial activity of nitro heterocycles is due to their metabolic reduction catalyzed by flavin-containing nitroreductases. Flavin mononucleotide (FMN) acts as a cofactor in deriving

Table 5
Anti-tubercular results of compounds **8a–j** against *M. tuberculosis* strain H37Rv

Entry	Compound	R^1	R^2	MIC (μg/ml)	Clog*P*[b]
1	**8a**	OH	OCH_3	8	0.4582
2	**8b**	H	NO_2	8	1.019
3	**8c**	NO_2	H	8	1.019
4	**8d**	OCH_3	NO_2	16	0.958
5	**8e**	F	Cl	0.25	2.132
6	**8f**	CF_3	H	—[a]	2.159
7	**8g**	OCH_3	H	—[a]	1.195
8	**8h**	F	OCH_3	—[a]	1.278
9	**8i**	OCH_3	F	—[a]	1.278
10	**8j**	OCH_3	OH	—[a]	0.4582
	Linezolid			1	

[a] Not active.
[b] Calculated using ChemDraw 11.0.

Table 6
Cytotoxicities of compounds **8a–j** against mammalian cell lines

Entry	Compound	IC_{50} values in (μM)	
		MRC-5	VERO
1	**8a**	182 ± 0.98	224 ± 0.65
2	**8b**	199 ± 0.99	326 ± 0.58
3	**8c**	213 ± 0.76	291 ± 0.97
4	**8d**	198 ± 0.68	176 ± 0.61
5	**8e**	254 ± 0.72	344 ± 0.58
6	**8f**	321 ± 0.68	289 ± 0.44
7	**8g**	146 ± 0.54	274 ± 0.89
8	**8h**	155 ± 0.81	225 ± 0.36
9	**8i**	324 ± 0.88	312 ± 0.79
10	**8j**	189 ± 0.97	174 ± 0.81
Ciprofloxacin (Standard)		181 ± 0.84	192 ± 0.73

MRC-5—Normal human lung cell line (ATCC No. CCL-171).
VERO—Normal monkey kidney cell line (ATCC No. CCL-81).

the reducing equivalents NADH or NADPH required for this process. This enzymatic reduction generates reactive intermediates which possess bactericidal properties before the final conversion to end products without bactericidal activity.[33] Therefore, it is proposed that the nitrofuran conjugates reported herein act through same mode of action as other nitrofuran drugs discussed above.

In conclusion, we have synthesized a series of nitrofuran–triazole conjugates employing click chemistry protocol which were evaluated for both antimicrobial and anti-tubercular activity. All the compounds showed good to moderate inhibitory and bactericidal effects over most of the Gram-positive and Gram-negative bacterial strains, respectively. Also the compounds were found to effectively inhibit biofilm formation responsible for resistance in bacteria thereby showing promising antimicrobial effect against the MRSA strain. Furthermore, the compound **8e** was found to be most active against *Mycobacterium tuberculosis* strain $H_{37}Rv$ and *B. subtilis*. Their lower cytotoxicities reflect their therapeutic potential for their growth in the field of antimicrobial agents. The work reported herein provides an insight in the development of novel antimicrobial and antitubercular agents effective over a wide range of pathogenic strains including the resistant ones.

Acknowledgements

The authors S.M.A.H., G.N.R., Y.P. and S.F. thank the CSIR, New Delhi and UGC, New Delhi for the award of research fellowships and Open Source Drug Discovery (OSDD), CSIR, New Delhi for financial assistance.

Supplementary data

Supplementary data (experimental procedures and spectroscopic characterization of the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.10.010.

References and notes

1. Ahmad, I.; Beg, A. Z. *J. Ethnopharmacol.* **2001**, *74*, 113.
2. (a) Payne, D. J.; Gwynn, M. N.; Holmes, D. J.; Pompliano, D. L. *Nat. Rev. Drug Disc.* **2006**, *6*, 29; (b) Miller, J. R.; Waldrop, G. L. *Expert Opin. Drug Disc.* **2010**, *5*, 145.
3. (a) Dalhoff, A. *Infection* **1994**, *22*, S111; (b) Abbanat, D.; Macielag, M.; Bush, K. *Expert Opin. Investig. Drugs* **2003**, *12*, 379; (c) Poole, K. *Curr. Opin. Microbiol.* **2001**, *4*, 500.
4. Olson, M. E.; Ceri, H.; Morck, D. W.; Buret, A. G.; Read, R. R. *Can. J. Vet. Res.* **2002**, *66*, 86.
5. Davies, D. *Nat. Rev. Drug Disc.* **2003**, *2*, 114.
6. Tewari, N.; Tiwari, V. K.; Tripathi, R. P.; Chaturvedi, V.; Srivastava, A.; Srivastava, R.; Shukla, P. K.; Chaturvedi, A. K.; Gaekwad, A.; Sinha, S.; Srivastava, B. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 329.
7. World Health Organisation, WHO, HTM/TB/2006.
8. World Health Organisation. Global tuberculosis control: Survellience, planning, financing; WHO work report 2004: Geneva, Switzerland.
9. *Tuberculosis: Pathogenesis, Protection and Control*; Bloom, B. R., Ed.; ASM Press: Washington, DC, 1994.
10. Zignol, M.; Hosseini, M. S.; Wright, A.; Lambregts-van Weezenbeek, C.; Nunn, P.; Watt, C. J.; Williams, B. G.; Dye, C. *J. Infect. Dis.* **2006**, *194*, 479.
11. (a) Kirilmis, C.; Ahmedzade, M.; Servi, S.; Koca, M.; Kizirgil, A.; Kazaz, C. *Eur. J. Med. Chem.* **2008**, *43*, 300; (b) Zanatta, N.; Alves, S. H.; Coelho, H. S.; Borchhardt, D. M.; Machado, P.; Flores, K. M.; Silva, F. M.; Spader, T. B.; Santurio, J. M.; Bonacorso, H. G.; Martins, M. A. *Bioorg. Med. Chem.* **1947**, *2007*, 15; (c) Kumar, P.; Narasimhan, B.; Sharma, D.; Judge, V.; Narang, R. *Eur. J. Med. Chem.* **1853**, *2009*, 44.
12. Kirilmis, C.; Koca, M.; Servi, S.; Gur, S. *Turk. J. Chem.* **2009**, *33*, 375.
13. (a) Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796; (b) Hofnung, M.; Quillardet, V. M.; Touati, E. *Res. Microbiol.* **2002**, *153*, 427.
14. Kedderis, G. L.; Miwa, G. T. *Drug Metab. Rev.* **1988**, *19*, 33.
15. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenco, G. E.; Hamel, J. C.; Schaadt, R. D.; Stepartand, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.
16. (a) Grana, G. *J. Surg. Oncol.* **2006**, *93*, 585; (b) Zhang, J.; Garrossian, M.; Gardner, D.; Garrossian, A.; Chang, Y. T.; Kim, Y. K.; Chang, C. W. T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1359.
17. Buckle, D. R.; Outred, D. J.; Rockell, C. J.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1983**, *26*, 251.
18. Joan, C. F. T.; Elizabeth, H.; Beatrice, M.; Daniel, P. B. *Antimicrob. Agents. Chemother.* **1998**, *42*, 313.
19. Simone, R. D.; Chini, M. G.; Bruno, I.; Riccio, R.; Mueller, D.; Werz, O.; Bifulco, G. *J. Med. Chem.* **2011**, *54*, 1565.
20. (a) Patpi, S. R.; Pulipati, L.; Yogeeswari, P.; Sriram, D.; Jain, N.; Sridhar, B.; Murthy, R.; Anjana, D. T.; Kalivendi, S. V.; Kanteveri, S. *J. Med. Chem.* **2012**, *55*, 3911; (b) Shanmugavelan, P.; Nagarajan, S.; Sathishkumar, M.; Ponnuswamy, A.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6844.
21. Bennet, I. S.; Brooks, G.; Broom, N. J. P.; Calvert, S. H.; Coleman, K.; Francois, I. *J. Antibiot.* **1991**, *44*, 969.
22. Williams, J. D.; Naber, K. G.; Bryskier, N. H.; Gould, I. M.; Periti, P.; Giamarellou, H.; Rouveix, B. *Int. J. Antimicrob. Agents* **2001**, *17*, 443.
23. Sotlis, M. J.; Yeh, H. J.; Cole, K. A.; Whittaker, N.; Werstro, R. P.; Kohn, E. C. *Drug Metab. Dispos.* **1996**, *24*, 799.
24. Reed, C. S.; Huisgens, R. W., III; Rogers, S. A.; Melander, C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6310.
25. Rogers, S. A.; Lindsey, E. A.; Whitehead, D. C.; Mullikin, T.; Melander, C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1257.
26. Kamal, A.; Swapna, P.; Shetti, R. V. C. R. N. C.; Shaik, A. B.; Rao, M. P. N.; Gupta, S. *Eur. J. Med. Chem.* **2013**, *62*, 661.
27. Kamal, A.; Ahmed, S. K.; Reddy, K. S.; Khan, M. N. A.; Shetty, R. V. C. R. N. C.; Siddhardha, B.; Murthy, U. S. N.; Khan, I. A.; Kumar, M.; Sharma, S.; Ram, A. B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5419.
28. Kamal, A.; Shetti, R. V. C. R. N. C.; Azeeza, S.; Swapna, P.; Khan, M. N. A.; Khan, I. A.; Sharma, S.; Abdullah, S. T. *Eur. J. Med. Chem.* **2011**, *46*, 893.
29. Kamal, A.; Murty, J. N. S. R. C.; Viswanath, A.; Sujitha, P.; Kumar, C. G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4891.
30. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
31. Details are available in Supplementary data.
32. Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, *4*, 413.
33. Mirzai, S.; Rafii, F.; Yasunaga, K.; Yoshunaga, K.; Sepehrizadeh, Z.; Kanno, S.; Tonegawa, Y.; Shahverdi, A. Z. *Comput. Biol. Med.* **2012**, *42*, 414.