Bioorganic & Medicinal Chemistry Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

One-pot synthesis of new triazole–Imidazo[2,1-*b*][1,3,4]thiadiazole hybrids via click chemistry and evaluation of their antitubercular activity

Jurupula Ramprasad [a], Nagabhushana Nayak [a], Udayakumar Dalimba [a,*], Perumal Yogeeswari [b], Dharmarajan Sriram [b]

[a] *Organic Chemistry Laboratory, Department of Chemistry, National Institute of Technology Karnataka, Surathkal, Srinivasanagar, Mangalore 575025, India*
[b] *Medicinal Chemistry and Drug Discovery Research Laboratory, Pharmacy Group, Birla Institute of Technology and Science-Pilani, Hyderabad Campus, Jawahar Nagar, Telangana 500078, India*

ARTICLE INFO

Article history:
Received 25 April 2015
Revised 18 July 2015
Accepted 5 August 2015
Available online xxxx

Keywords:
Mycobacterium tuberculosis
Imidazo[2,1-*b*][1,3,4]thiadiazole
1,2,3-Triazole
Click chemistry
Drug-likeness score

ABSTRACT

A new series of triazole–imidazo[2,1-*b*][1,3,4]thiadiazole hybrids (**6a**–**s**, **7a**) were designed by a molecular hybridisation approach and the target molecules were synthesized via one pot click chemistry protocol. All the intermediates and final molecules were characterised using spectral methods and one of the target compounds (**6c**) was analysed by the single crystal XRD study. The derivatives were screened for their antimycobacterial activity against *Mycobacterium tuberculosis* H_{37}Rv strain. Two compounds, **6f** and **6n**, demonstrated significant growth inhibitory activity against the bacterial strain with a MIC of 3.125 μg/mL. The presence of chloro substituent on the imidazo[2,1-*b*][1,3,4]thiadiazole ring and ethyl, benzyl or cyanomethylene groups on the 1,2,3-triazole ring enhance the inhibition activity of the molecules. The active compounds are not toxic to a normal cell line which signifies the lack of general cellular toxicity of these compounds.

Tuberculosis (TB) is one of the dominant killer diseases[1] and it causes huge amount of human deaths in spite of the availability of more than 20 antiTB drugs and the Bacille Calmette Guerin (BCG) antiTB vaccine.[2] The emergence of the extensively drug-resistant tuberculosis (XDR-TB) and multidrug-resistant tuberculosis (MDR-TB), against which the traditional anti-TB drugs show limited efficacy,[3] further cause serious problem in TB control. According to WHO global tuberculosis report 2014,[4] globally 3.5% of new and 20.5% of previously treated TB cases were estimated to be multidrug-resistant. This translates into an estimated 480,000 people having developed MDR-TB in 2013. Thus there is an emergent need to develop more effective drugs with minimum side effects to treat XDR-TB and MDR-TB. In view of this, a great deal of research work is being devoted to identify newer molecular entities which are active against the bacterial strains. The most important molecular design strategies in this direction are (i) structural modification of the known drug molecule;[5] (ii) computer-aided drug design based on the study on ligand–protein interaction;[6] (iii) hybridisation of two active pharmacophoric units into a single molecular framework[7,8] and (iv) the random screening of different structural units and proceeding in an observed window of anti-TB activity,[9–12] all these approaches are being considered as promising to develop effective drugs.

The 1,2,3-triazole derivatives find great importance in the medicinal chemistry research due to their important biological actions in addition to their synthetic applications.[13,14] The triazole ring is a core structural moiety in some of the important drugs like tazobactam and cefatrizine (which are used for bacterial infections), carboxyamidotriazole (which is used for cancer treatment) and rufinamide (which is used as an anticonvulsant). A few recent Letters demonstrated the promising antitubercular activity of 1,2,3-triazole derivatives.[15,16] For example, a series of (*E*)-*N*1-[(1-aryl)-1*H*-1,2,3-triazole-4-yl)methylene]isonicotinoylhydrazide (I) based molecules exhibit outstanding antitubercular activity, several of them possess MIC value in the range 2.5–0.62 μg/mL.[17] The triazole based antitubercular agent 6-hydroxy-3-(1-(2-((4-morpholinophenyl)amino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)-2-phenylbenzofuran-5-carboxylic acid (II, I-A09) which is presently under preclinical trials, is viewed as a promising class of pharmacophore to provide effective drug candidates.[18] Further, Patpi et al. designed a set of 1,2,3-triazole based hybrid molecules following the molecular hybridisation strategy and among these,

* Corresponding author. Tel.: +91 824 2473207; fax: +91 824 2474033.
E-mail addresses: udayaravi80@gmail.com, udayakumar@nitk.ac.in (U. Dalimba).

http://dx.doi.org/10.1016/j.bmcl.2015.08.009
0960-894X/

compounds 4-(4-(*tert*-butyl)phenyl)-1-(1-(dibenzo[*b*,*d*]thiophen-2-yl)ethyl)-1*H*-1,2,3-triazole (III) and 4-(2-chloro-4-fluorophenyl)-1-(1-(dibenzo[*b*,*d*]thiophen-2-yl)ethyl)-1*H*-1,2,3-triazole (IV) exhibited excellent antitubercular activity with MIC of 0.78 μg/mL.[19] Similarly, the imidazole and thiadiazole moieties also are key scaffolds in the medicinal chemistry research and several drugs containing these moieties are available in the market. Imidazole containing Pretomanid (PA-824) (nitro imidazopyran) is potent against both replicating and hypoxic, non-replicating *Mycobacterium tuberculosis* (*Mtb*).[20] Megazol which acts as antiparasitic, contain both 1,3,4-thiadiazole and imidazole rings. However, the amalgamation of these two molecular entities as imidazo[2,1-*b*][1,3,4]thiadiazole (ITD) ring resulted an active pharmacophore possessing a broad spectrum of pharmacological activity.[21–24] A few ITD derivatives carrying other active pharmacophores particularly at C-5 (V and (*Z*)-2-(4-oxo-5-((6-phenyl-2-(trifluoro methyl)imidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)methylene)-2-thioxothiazolidin-3-yl)acetic acid (VI)) have been found to possess good activity against *Mtb* H_{37}Rv strain.[25,26] For instance, Kolavi et al. reported the synthesis and antitubercular evaluation of a series of ITD derivatives carrying a hydroxy methyl group at position-5 (VII).[27] In our previous work, we demonstrated the excellent antitubercular activity (MIC of 3.125 μg/mL) of a series of 2-(2-substituted-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)-1*H*-benzimidazole derivatives (VIII).[28] Thus, the promising antitubercular activity exhibited by imidazo[2,1-*b*][1,3,4]thiadiazole and 1,2,3-triazole systems (Fig. 1) prompted us to integrate these two pharmacophores in a single molecular framework and to explore the effects of this molecular hybridisation on their activity against *Mtb* H_{37}Rv strain. In view of this, we synthesized a new library of 1,2,3-triazole containing imidazo[2,1-*b*][1,3,4]thiadiazoles (**6a**–**s**, **7a**) and evaluated their antitubercular activity.

Scheme 1 depicts the synthetic route of new 1,2,3-triazole-imidazo[2,1-*b*][1,3,4]thiadiazole hybrids (**6a**–**s**, **7a**). The 6-aryl-2-methylimidazo[2,1-*b*][1,3,4]thiadiazoles (**2a**–**c**) were synthesized by treating compound **1a** with corresponding phenacyl bromide derivatives. These compounds were then subjected to Vilsmeier–Haack formylation reaction to yield 6-aryl-2-methylimidazo [2,1-*b*][1,3,4]thiadiazole-5-carboxaldehydes (**3a**–**c**).[28] The key intermediates, 6-aryl-2-methylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl) methanol (**4a**–**c**) were synthesized by reducing the corresponding aldehyde intermediates (**3a**–**c)** using $NaBH_4$ as the reducing agent. Intermediates **4a**–**c** were then treated with propargyl bromide in the presence of sodium hydride to yield 6-aryl-2-methyl-5-((prop-2-ynyloxy)methyl)imidazo[2,1-*b*][1,3,4]thiadiazoles (**5a**–**c**). Finally, the target compounds (**6a**–**s**) were synthesized by following Huisgen 1,3-dipolar cycloaddition reaction (click reaction) in which alkyne intermediates (**5a**–**c**) were treated with different substituted alkyl bromides in the presence of sodium azide.[29] The ester group in compound **6m** was hydrolysed using LiOH to get the target compound **7a**.

The structure of newly synthesized intermediates and target compounds was confirmed by ^{1}H NMR, ^{13}C NMR, mass spectral and elemental analyses. For instance, the ^{1}H NMR spectrum of **6n** showed a singlet at δ 7.5 ppm due to –CH proton of the triazole ring whereas a quartet at δ 4.40 ppm and a triplet at δ 1.55 ppm correspond to methylene and methyl protons of the N-ethyl group, respectively. The methylene protons of $-CH_2$-O-CH_2- bridge appeared as two separate singlets at δ 4.93 and 4.79 ppm in which the singlet at a slightly higher chemical shift value corresponds to

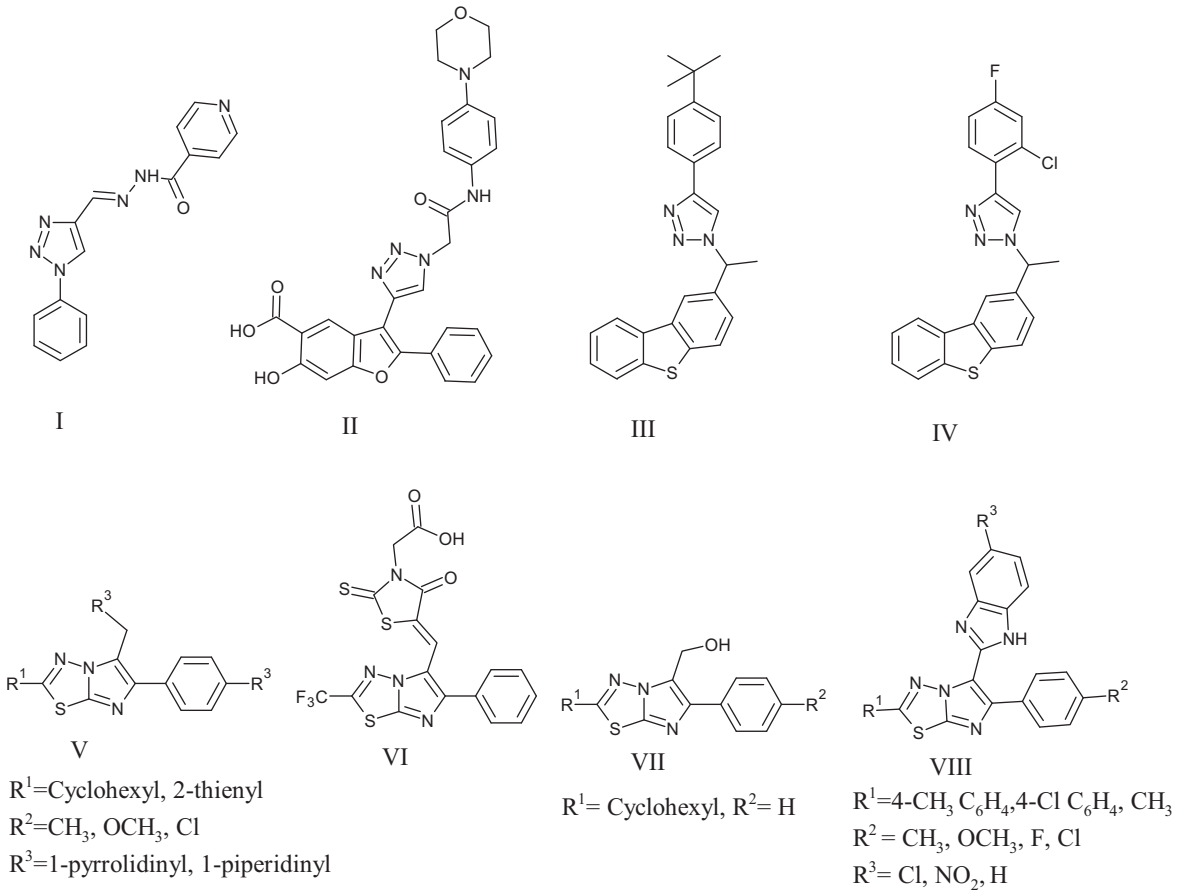
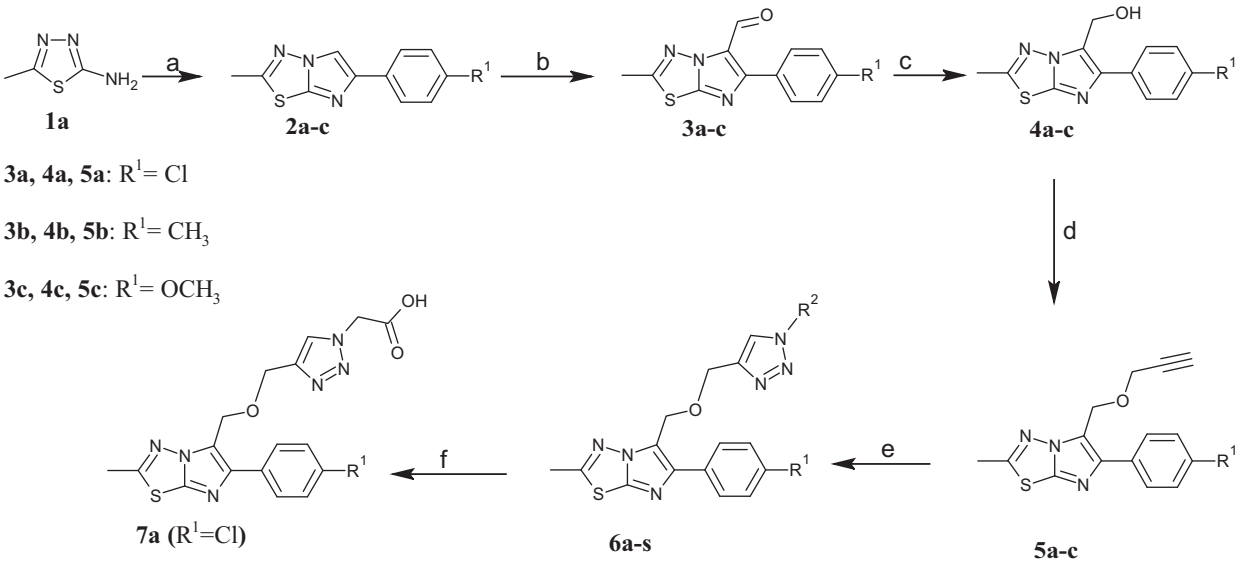


Figure 1. Structures of some representative imidazo[2,1-*b*][1,3,4]thiadiazole and 1,2,3-triazole containing antitubercular agents.



Scheme 1. Reagents and conditions: (a) phenacyl bromide, ethanol, 80–85 °C, 24 h, yield: 80–82%; (b) DMF, $POCl_3$, 60 °C, 6 h, yield: 82–85%; (c) $NaBH_4$, MeOH, 0 °C–rt, 4 h, yield: 92–96%; (d) propargyl bromide, NaH, THF, 0 °C–rt, 4 h, yield: 96–98%; (e) R^2Br, NaN_3, sodium ascorbate, copper(II) sulfate, *t*-BuOH and water, rt, 24 h, yield: 82–92%; (f) $LiOH{\cdot}H_2O$, THF, MeOH, water, rt, 5 h, yield: 82%.

the methylene group attached to the 1,2,3-triazole ring. In addition, the spectrum displayed a singlet at δ 2.75 ppm due to methyl group present at position-2 of the ITD ring. The ^{13}C NMR spectrum of **6n** displayed all characteristic peaks corresponding to its molecular structure; the two methylene carbons of $–CH_2–O–CH_2–$ bridge appeared at δ 63.88 and 60.98 ppm whereas peaks at δ 45.3 and 15.5 ppm represent methylene and methyl carbons of the ethyl group, respectively. The characterisation data of all the target compounds are given in the experimental part while their physical data are tabulated in Table 1. Some representative spectra are given in Supplementary information.

The three dimensional structure of one of the target compounds, **6c** was evidenced by single crystal X-ray diffraction studies. The single crystals of **6c** were grown from methanol and chloroform (1:1) solvent mixture by the slow evaporation of the solvent at room temperature. A crystal of suitable size was mounted and single-crystal data was collected at room temperature. The crystal structure was solved and refined by direct methods using SHELXL-2013 package. The hydrogens were fixed in geometrically calculated positions and refined isotropically. The molecule crystallises in the triclinic system with *P*-1 space group. The crystal structure (ORTEP diagram) and crystal data of the compound are given in Figure 2. The asymmetric unit contains two molecules of **6c** that are held by $C_{18}—N_{12}$ short contact. The crystal packing structure of **6c** is given in Supporting information.

Table 1
Structural features, log*P*/C log*P* values and drug-likeness score of target compounds (**6a–s** and **7a**)

Product	R^1	R^2	Log*P*/C log*P*	Drug-likeness score
6a	OCH_3	CH_2-COOEt	3.51/1.65	0.31
6b	OCH_3	CH_2-CH_3	3.98/1.55	0.35
6c	OCH_3	CH_2-CN	3.39/0.49	0.05
6d	OCH_3	2-Fluorobenzyl	5.54/2.93	0.52
6e	OCH_3	4-Fluorobenzyl	5.54/2.93	0.65
6f	OCH_3	CH_2-C_6H_5	5.38/2.79	0.41
6g	CH_3	CH_2-COOEt	4.13/2.14	0.14
6h	CH_3	CH_2-CH_3	4.6/2.04	0.28
6i	CH_3	CH_2-CN	4.00/0.98	−0.02
6j	CH_3	2-Fluorobenzyl	6.15/3.42	0.34
6k	CH_3	4-Fluorobenzyl	6.15/3.42	0.49
6l	CH_3	CH_2-C_6H_5	5.99/3.28	0.28
6m	Cl	CH_2-COOEt	4.2/2.35	0.76
6n	Cl	CH_2-CH_3	4.67/2.25	0.85
6o	Cl	$CH(CH_3)_2$	4.99/2.56	1.07
6p	Cl	CH_2-CN	4.07/1.19	0.54
6q	Cl	2-Fluorobenzyl	6.22/3.63	0.82
6r	Cl	4-Fluorobenzyl	6.22/3.63	0.75
6s	Cl	CH_2-C_6H_5	6.06/3.49	1.00
7a	Cl	CH_2-COOH	3.6/1.492	1.21

All the target molecules (**6a–s** and **7a**) were screened against *Mtb* $H_{37}Rv$ (ATCC27294) using Agar dilution method. Their antimycobacterial activity was evaluated in terms of minimum inhibitory concentration (MIC) values. The MIC values in μg/mL of **6a–s** and **7a** along with those of standard drugs for comparison are presented in Figure 3. The MIC values of the compounds are in the range 3.125–50.0 μg/mL. It is evident that among twenty compounds, **6f** and **6n** show potent anti-tubercular activity with MIC of 3.125 μg/mL. The MIC of these two compounds is comparable with that of the standard drug, ethambutol. Compound **6p** showed moderate inhibition activity with MIC of 6.25 μg/mL. The nature of the substituent on imidazo[2,1-*b*][1,3,4]thiadiazole (R^1) and 1,2,3-triazole (R^2) rings affect the activity of the compounds. Most of the chloro or methoxy substituted derivatives exhibited superior activity than their methyl substituted analogues. All the methyl substituted derivatives (**6g–l**) showed MIC $\geqslant$25 μg/mL irrespective of the nature of the substituent at R^2 whereas a few methoxy and chloro analogues exhibited lower MIC values (3.125–12.5 μg/mL). This general structure–activity relationship signifies the contribution of chloro/methoxy substituent (R^1) towards the inhibition activity of the molecules. The presence of ethyl or benzyl groups on the 1,2,3-triazole ring enhances the inhibition activity of the molecules, which is evident by the significant activity shown by compounds **6n** and **6f**. Further, methyl analogues (**6h** and **6l**) with these substituents also exhibited moderate activity (MIC = 25 μg/mL). Other substituents like CH_2CN, CH_2COOEt and 4-fluorobenzyl on the 1,2,3-triazole ring also contributed in enhancing the activity of the molecules. The 4-fluorobenzyl derivatives (**6e**, **6k** and **6r**) are either equipotent or two fold more potent than respective 2-fluorobenzyl analogues (**6d**, **6j** and **6q**) which reveals the dependence of the activity on the position of the fluoro substitution. The hydrolysis of the ester functionality on the 1,2,3-triazole ring (**6m**, MIC = 12.5 μg/mL) to a carboxylic acid group substantially decreased the potency of the molecule (**7a**, MIC = 50 μg/mL). The

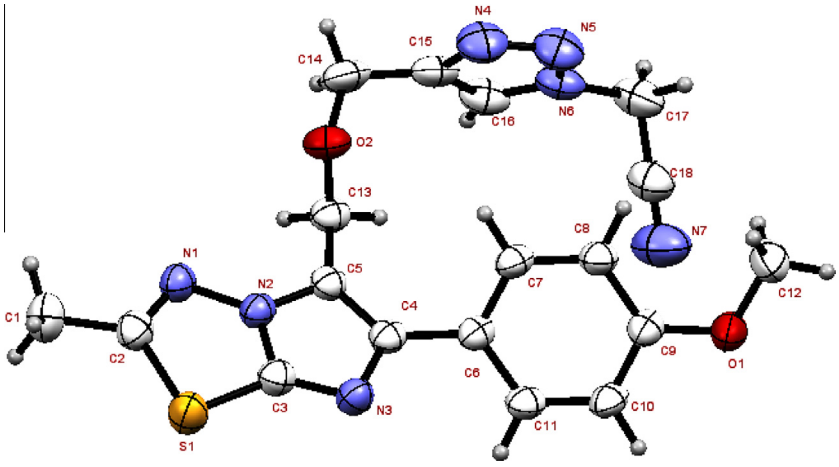


Figure 2. ORTEP diagram showing the X-ray crystal structure of compound **6c**. (Crystal data: CCDC no. 1059072; formula: $C_{18}H_{17}N_7O_2S$; M = 395.45; unit cell parameters: a, b, c (Å) = 7.664 (3), 8.644 (3), 28.420 (10); α, β, γ = 85.80 (2)°, 89.38 (2)°, 72.46 (19)°; volume (Å^3): 1790.3 (11); T: 296 K; crystal system: triclinic; space group: P-1; Z = 4; R_1 = 0.0424; wR_2 = 0.1466; radiation type: Mo Kα; μ (mm^{-1}): 0.213; radiation wavelength (Å): 0.71073.

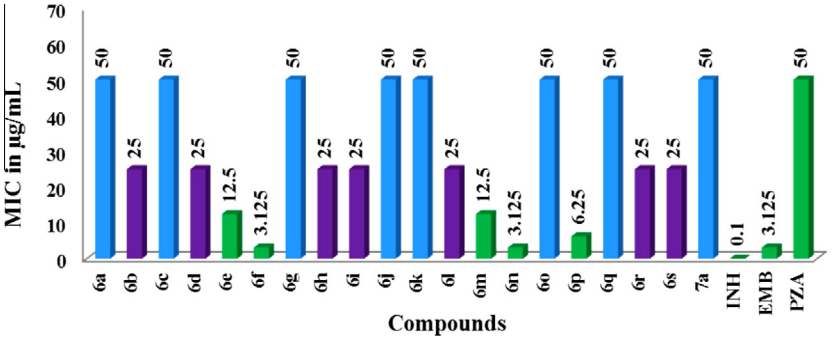


Figure 3. The antitubercular activity of **6a–s** and **7a** against *M. tuberculosis* $H_{37}RV$ (INH: isoniazid; EMB: ethambutol; PZA: pyrazinamide).

substitution of different groups at R^1 and R^2 affect the lipophilicity of the molecules (Table 1). However, we did not observe a general relationship between lipophilicity and the activity of the compounds. Nevertheless, it is interesting to compare the log*P*/*C*log*P* values of the active molecules and to account for the activity based on their lipophilicity. The *C*log*P* values of the active molecules are in the range 2.2–2.9 with log*P* values in the range 4–5.5. Though ethyl and benzyl substituents (R^2) are found to enhance the activity, ethyl derivative **6b** and benzyl derivative **6s** showed only a moderate activity (MIC = 25 µg/mL) which could be rationalised based on the lower *C*log*P* value for **6b** and a higher value for **6s**. A similar relationship between lipophilicity and activity was observed in other active derivatives as well which contain substituents like CH_2COOEt and 4-fluorobenzyl group. Only those derivatives (viz. **6e** and **6m**), whose lipophilicity falls in the above mentioned values have shown good activity whereas their analogues with higher (**6r**) or lower (**6s**) values have shown relatively a lower activity. Also the most promising antitubercular compounds **6e**, **6f**, **6m**, **6n** and **6p** exhibited positive drug-likeness score[30] of 0.65, 0.41, 0.76, 0.85 and 0.54, respectively, (Table 1). So it may be concluded that in addition to the structural features, which play a major role, the lipophilicity factor also influences the inhibition activity of the molecules. This information on structure/lipophilicity–activity relationship explored in the present study could be helpful in further structural modification and development of new 1,2,3-triazole-imidazo[2,1-*b*][1,3,4] thiadiazole hybrids as potent antitubercular agents.

The in vitro cytotoxicity of the active compounds (MIC ⩽12.5 µg/mL) were evaluated by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay against NIH 3T3 mouse embryonic fibroblasts cell line. The graphical representation of the cell growth inhibition by the compounds at a concentration of 50 µg/mL is shown in Figure 4. The compounds did not show any toxicity to the cell line signifying the lack of general cellular toxicity.

In conclusion, a series of twenty new 1,2,3-triazole-imidazo [2,1-*b*][1,3,4]thiadiazole hybrids (**6a–s**, **7a**) were designed by molecular hybridisation approach and were synthesized using a click chemistry reaction. These compounds were characterised by

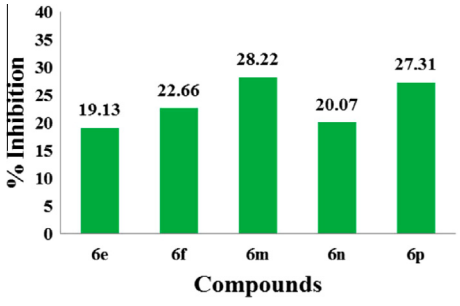


Figure 4. Growth inhibition activity of active compounds (at a concentration of 50 µg/mL) against NIH 3T3 cell line.

^{1}H NMR, ^{13}C NMR, mass spectroscopic techniques and elemental analysis. In the anti-tubercular screening, compounds **6f** and **6n** exhibited significant activity against the growth of *Mtb* with MIC of 3.125 μg/mL. A moderate activity with MIC of 6.25 μg/mL was observed for compound **6p**. The structure–activity relationship revealed that the 4-chlorophenyl group contributes significantly in enhancing the inhibition activity of the molecules. Further, substituents like ethyl, benzyl, 4-fluorobenzyl, CH_2CN and CH_2COOEt on the 1,2,3-triazole ring enhance the anti-tubercular activity. The active molecules exhibited positive drug-likeness score and their *C*log*P* values are in the range 2.2–2.9. Also, none of the active molecules is toxic to a normal cell line. Hence, these compounds with significant anti-TB activity could serve as promising lead molecules for further generation of potent antitubercular agents. Further, the present study reveals that the molecular hybridisation approach could be a promising strategy for designing potent antitubercular agents.

Acknowledgments

Authors are thankful to NITK, Surathkal for providing the research facilities and to Dr. Reddy's Institute of Life Sciences, Hyderabad Central University for providing NMR and mass spectral analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.08.009.

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