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ORIGINAL PAPER

Synthesis of novel 1,2,3-triazoles bearing 2,4 thiazolidinediones conjugates and their biological evaluation

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Abstract

Searching for new active molecules against *M. Bovis BCG* and *Mycobacterium tuberculosis (MTB) H37Ra*, a focused of 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates have been efficiently prepared via a click chemistry approach cyclocondensation of 4-amino-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**4**), aryl aldehyde (**5a–l**), and mercapto acetic acid (**6**) with good to promising yields. The newly synthesized compounds were tested against drug-sensitive *MTB* and *BCG*. In particular, compounds **8g**, **8h**, **8j** and **8l** are highly potent against both the strains with IC_{90} values in the range of 1.20–2.70 and 1.24–2.65 µg/mL, respectively. Based on the results from the antitubercular activity, SAR for the synthesized series has been developed. Most of the active compounds were non-cytotoxic against MCF-7, HCT 116 and A549 cell lines. Most active compounds were having a higher selectively index, which suggested that these compounds were highly potent.

Keywords 1,2,3-Triazoles · 2,4 Thiazolidinedione · Amide and Ethereal linkage · Anti-mycobacterial activity · Cytotoxicity study

Introduction

Tuberculosis (TB) is a life-threatening syndrome that emerges as a global health issue, due to this second most important reason of death among the infectious diseases after HIV [1]. World Health Organization (WHO) report, expected 2 million deaths occur per year and 10 million latest cases of TB [2]. Additional > 30 million lives will be claimed by tubercular between 2000 and 2020 [3]. Mycobacterium tuberculosis (*MTB*) strains together with co-infection with HIV is another disadvantage of tuberculosis [4]. The *M. Bovis*Bacille Calmette-Guerin (*M. Bovis BCG*) injection has been among the most frequently administrated worldwide [5] and the only attenuated live vaccine [6]. In addition to this, totally drug-resistant TB (TDR-TB) has recently arisen which is resistant to all clinical drugs [7]. Delamanid (OPC-67683) and bedaquiline (TMC207) are the two drugs agreed with by the US FDA for the multi-drug-resistant tuberculosis (MDR-TB) treatment [8, 9]; however there are no present medicinal drugs under clinical trials. Due to this, there is an insistent need for novel, safe and effective anti-mycobacterial drugs which will efficiently treat XDR and MDR tuberculosis.

1,2,3-Triazole, a five-membered *N*-heterocyclic compounds, is a very well-known bioactive molecules constructed by the copper-catalyzed azide-alkyne by cycloaddition(CuAAC) reaction, which is popular as a click chemistry reaction [10]. Among the various 1,2,3- triazoles, 1,4-disubstituted-1,2,3-triazole derivatives have been found to have broad spectrum applications and is used in numerous fields including material science [11], polymer chemistry [12], and drug discovery [13]. Literature survey revealed that, 1,2,3-triazole-based molecules display various therapeutic activities such as anti-inflammatory [14], antibacterial [15], anti-fungal [16], anti-convulsant [17], antiproliferative [18], antitubercular [19–22], anti-HIV [23] and anticancer [24]. Some molecular structures of antitubercular agents bearing 1,2,3-triazolyl scaffolds are shown in Fig. 1.

Thiazolidinediones is a privileged five-membered heteroatomic compound containing sulfur, oxygen and nitrogen as heteroatoms. Thiazolidinediones and its derivatives offer high degree of structural diversity that has proven their usefulness for searching new therapeutic leads. Thiazolidinediones are well-known class of biological active substances that became basic for the whole number of innovative

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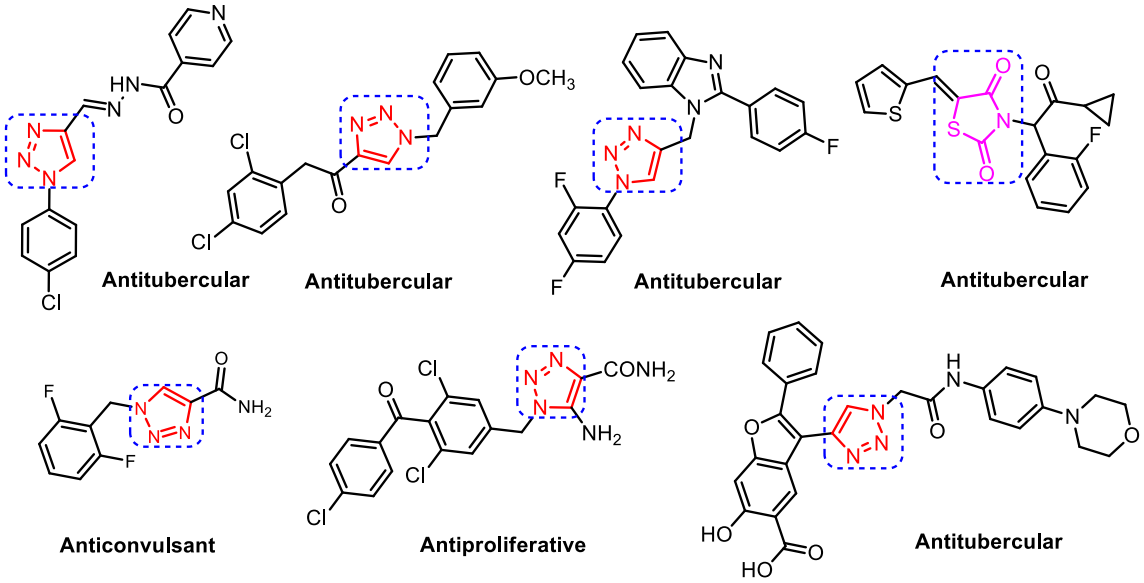


Fig. 1 1,2,3-triazole-incorporated bioactive molecules

medicinal agents, such as anticancer activity [25], anti-inflammatory [26], antimicrobial [27], anti-mycobacterial agents [28], antitrypanosomal/antiviral [29], inhibitors of protein tyrosine phosphatase 1B (PTP1B) [30], estrogen-related receptor 1 [31], cyclooxygenase-2 (COX-2) [32], pim kinase 1 [33], aldose reductase (ALR2) [34], hypoglycemic [35], murD ligase [36], DNA sensors [37], pim-1 and pim-2 protein kinases [38], leishmania pteridine reductase 1 [39] and PI3Ka/MEK1 [40].

The copper-catalyzed 1,3-dipolar cycloaddition of organic azides and terminal alkynes has been reported by using various methods [41, 42] and environmentally benign catalyst such as Fe_3O_4/silicalite-1/PVA/Cu(I) nanocomposites [43], Cu_2O/Agar@Fe_3O_4 [44], [bmim][BF_4] [45, 46], [Bmim]OH [47], (SNILCu(II)) [48], ([Hmim]TFA) [49] and [C8dabco][N(CN)2] [50] and DBU based ionic liquids [51]. The design of 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates are mainly divided into three different sections as depicted in Fig. 2. The first one is the main backbone of the design strategy that is 2,4-thiazolidinediones bioactive unit. It helps to enhance the pharmacophoric properties as they exhibits drug-like properties. The second backbone is showing 1,2,3-triazoles with amide and ethereal linkages which is responsible for biological activity. Last of all, the aryl group part with diverse substitutional unit is responsible for the lipophilicity control while contributing highly potent pharmacological part due to existence of various functional groups.

Considering the therapeutic significance of the above, herein, we have planned and synthesized 1,2,3-triazoles-bearing 2,4 thiazolidinedione by accumulating amide linked substituted variant unit, 1,2,3-triazoles and 2,4 thiazolidinedione moiety in a single molecular framework with hope to obtain better antitubercular agents with reduced side effects.

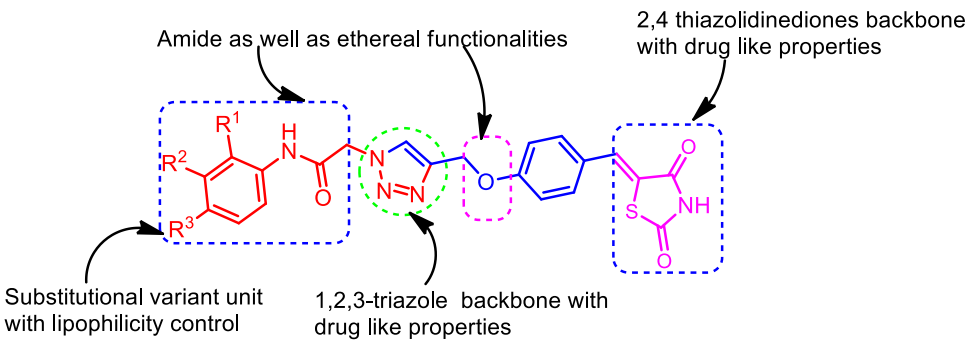


Fig. 2 Molecular design approach for the preparation of 1,2,3-triazoles bearing 2,4 thiazolidinedione moiety

Results and discussion

Chemistry

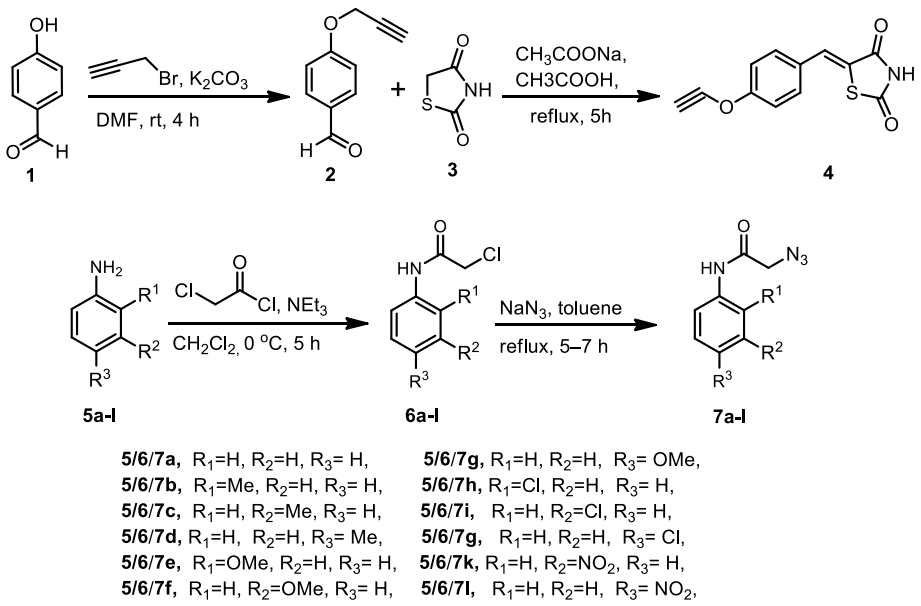
There are numerous reports on the synthesis of 1,4-disubstituted- 1,2,3-triazoles bearing amide functionality and displaying broad spectrum of biological activities [52] recently, Ferroni et al. developed triazoles as nonsteroidal anti-androgens for prostate cancer treatment [53]. On the basis of these findings, we designed small 1,2,3-triazoles with amide linkage in their structures.

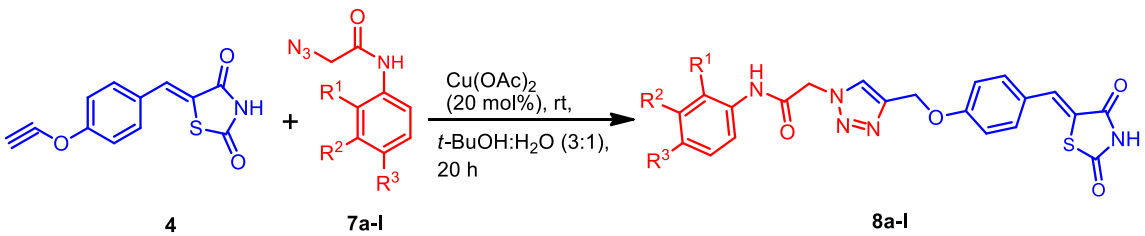
Initially, the starting materials, 4-(prop-2-yn-1-yloxy) benzaldehyde**2** were prepared from commercially available 4-hydroxybenzaldehyde **1** and propargyl bromide in the presence of K_2CO_3 as a base in *N,N*-dimethylformamide (DMF) afforded 4-(prop-2-yn-1-yloxy)benzaldehyde in excellent yield (93%). In the next step cyclocondensation reaction of 4-(prop-2-yn-1-yloxy)benzaldehyde **2** with 2,4-thiazolidinedione **3** using sodium acetate as a base in acetic acid to give 88% yield of 5-(4-(ethynyloxy)benzylidene)thiazolidine-2,4-dione **4**. The synthesis of 2-Azido-*N*-phenylacetamides [54] 7**a–l** from their corresponding anilines via chloroacetylation using chloroacetyl chloride, followed by nucleophilic substitution with sodium azide in good to excellent yields (84–95%) (Scheme 1).

The Huisgen CuAAC reaction has been performed on 5-(4(ethynyloxy)benzylidene)thiazolidine-2,4-dione 4with 2-Azido-*N*-phenylacetamides 7a-l in the presence of $Cu(OAc)_2$ in *t*-BuOH–H_2O (3:1) at room temperature for 20 h affording 2-(4-((4-((2,4-dioxothiazolidin-5 ylidene) methyl)phenoxy)methyl)-*1H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide derivatives 8a-l in good to excellent (72–89%) yield (Scheme 2).The synthetic sequence is depicted in Scheme 2.

Comparison of $Cu(OAc)_2$ catalyst with previous reported protocol

We have also compare the $Cu(OAc)_2$ catalyst with other reported catalysts for the preparation of 1,2,3-triazoles-incorporated 2,4 thiazolidinedione derivative (Table 1, entry 9).





Scheme 1 Synthesis of alkynes **2** and 2-azido-*N*-phenylacetamides **5a–l**

Scheme 2 Synthesis of 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates **8a–l**

Table 1 Comparative catalytic performance of the $Cu(OAc)_2$ with other previously reported catalysts

Entry	Catalyst	Time (min)	Yield (%)	Solvent/condition	Refs.
1	$CuSO_4.5H_2O$, (1 mol.%) Sodium ascorbate (5 mol.%)	8 h	96	t-BuOH:H_2O (1:2)	[55]
2	Ag_2CO_3 (10 mol.%) CPyCl (10 mol.%)	10 h	86	H_2O	[56]
3	CuI (20 mol.%) LiO-t-Bu (2.0 eq.)	4 h	84	Dioxane (0.1 M)	[57]
4	TEMPO	12 h	80	H_2O	[58]
5	DMF, air	6 h	80	–	[59]
6	$[Cu(MeCN)_4]PF_6$ (1 mol.%) 1,10-phenanthroline (1 mol.%)	10 h	82	$AgNO_3$, pyridine	[60]
7	$Cu(ClO_4)_2$ NaI	8 h	84	TEA, CH_3CN	[61]
8	CuI (5 mol.%) TBTA (5 mol.%) XPhos-Pd-G3 (1 mol.%)	15 h	88	KOAc, THF	[62]
11	$Cu(OAc)_2$ (20 mol.%)	20 h	89	t-BuOH:H_2O (3:1)	Present work

[a]Reaction conditions: **4a** (1 mmol), **7a** (1 mmol) and $Cu(OAc)_2$ (20 mmol) in *t*-BuOH-H_2O (3:1) at room temperature

All the newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS techniques. In the ^{1}H NMR spectra of representative compound **8a** displays two sharp singlet at δ 5.30 and 5.36 ppm as a methylene protons of $–CH_2–CO–$ and $–CH_2–O–$, respectively. The singlet peak appeared at 7.97 due to the –CH = C proton. The singlet observed at δ 8.30 ppm due to proton present on the triazole ring and singlet at 10.49 and 9.41 ppm assigned for the –CO–NH– of amide and -CO–NH–CO of 2,4 thiazolidinedione ring. In ^{13}CNMR spectra, the peaks appears at δ 48.91 ppm shows the methylene carbon connected to the nitrogen of triazole ring and peak at 56.93 ppm assigned for methylene carbon near to oxygen, peak at 143.31 ppm for the triazole quaternary carbon and peak at 161.25, 166.90, 169.55 ppm indicating carbonyl carbon for the –CO–NH- of amide and –CO–NH–CO of 2,4 thiazolidinedione ring in compound **8a.** In addition the formation of compound **8a** was confirmed by the HRMS spectrum and the calculated $[M + H]^+$ was 436.3442 and in HRMS, the $[M + H]^+$ observed peak at 436.3420.

In the first step reaction of alkyne to the Cu(I) metal to form a Cu(I)-alkyne π-complex (**A**). The generation of the Cu(I)-acetylide species permits the subsequent displacement of the ligand with azide and results in a dimeric copper species (**B**). Azide complexation induces the nucleophile attack at the N-3 with the C-4 acetylide. The resulting metallocycle (**C**) give the copper-triazole complex (**D**). Finally, protonation of the copper-triazole complex by water and disassociation of the labile copper complex gives the 1,4-disubstituted 1,2,3-trazole (**E**) and regeneration of catalyst (Fig. 3).

Biological evaluation

In vitro Anti-mycobacterial activity evaluation

The novel synthesized 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates (**8a–l**) were evaluated for in vitro anti-mycobacterial activity against *M. bovis BCG* (ATCC 35743) and *MTB H37Ra* (ATCC 25177) in liquid medium [63]. We have explored the eminent XTT Reduction Menadione assay (XRMA) of anti-mycobacterial screening protocol employing first-line anti-mycobacterial rifampicin drug as a standard reference and the IC_{50} and IC_{90} values are presented in Table 2.

The 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates **8g**, **8h**, **8j** and **8l** shows promising anti-mycobacterial activity against *M. bovis BCG* and *MTB* strain with IC_{90} range 1.20–2.70 and 1.24–2.65 µg/mL, respectively. However, the remaining 1,2,3-triazoles-incorporated 2,4-thiazolidinedione derivatives **8a, 8b**, **8c**, **8d**, **8e**, **8f**, **8i** and **8 k** exhibit lower anti-mycobacterial activity against *M. bovis BCG* and *MTB* strain with $IC_{90} => 30$ µg/mL with reference to rifampicin as a standard reference.

Structure activity relationship (SAR)

According to the data, the 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates exhibits promising anti-mycobacterial activity and the outcomes are presented in Table 1. In compounds **(8a–l)**, the 2,4 thiazolidinedione moiety attached to aryl ring is constant and modifications in the amides aryl unit shows difference in the anti-mycobacterial activity against the *M. bovis* BCG and *MTB* strain. Firstly,

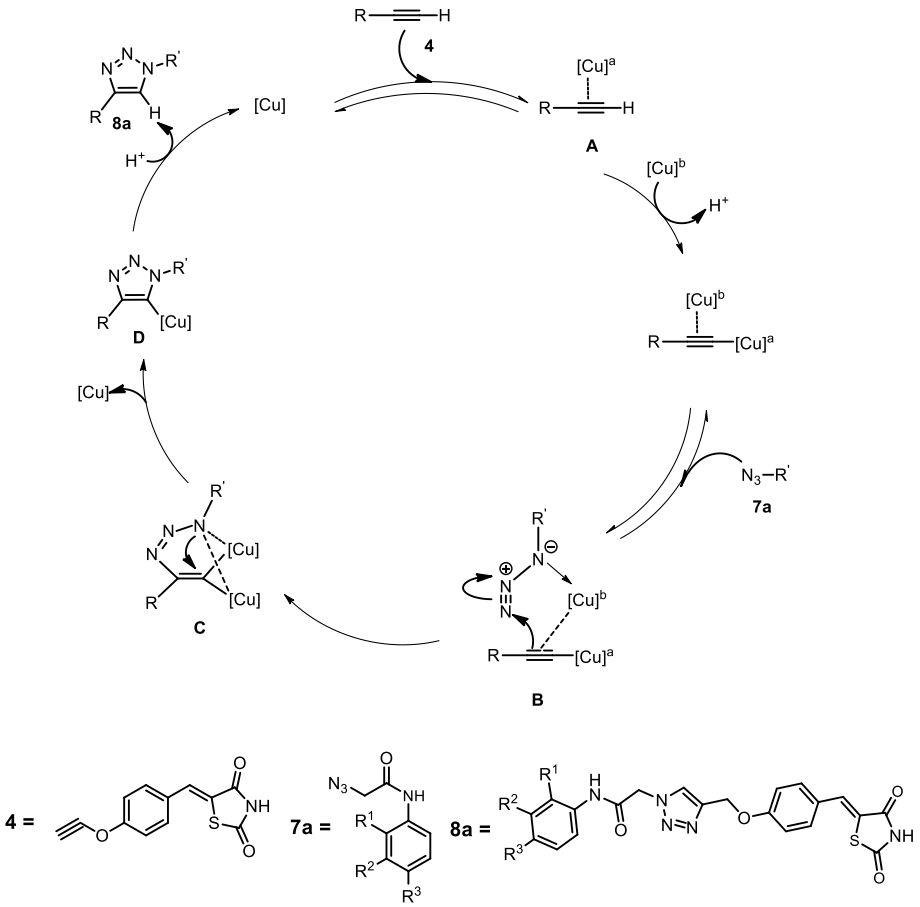


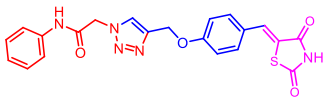
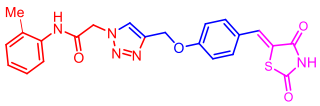
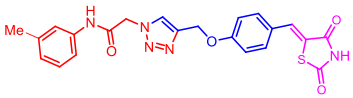
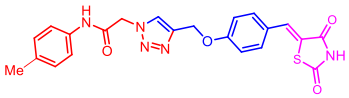
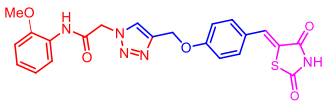
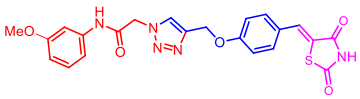
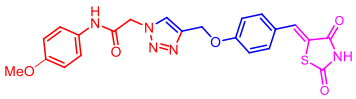
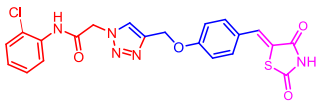
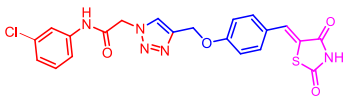
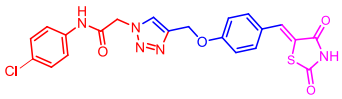
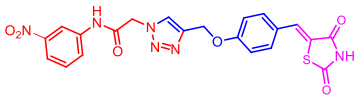
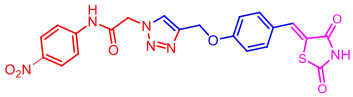
Fig. 3 Plausible mechanisms for the CuAAC reaction

we will discuss the anti-mycobacterial activity of synthesized 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates against *M. bovis* BCG strain. From the series **(8a–l)**, compound **8a** without any substituent on aryl ring displays lesser antitubercular activity with IC_{90} value > 30 µg/mL against *M. bovis BCG* strain in comparison with rifampicin as a standard and results are displayed in Table 1. Compounds **8b** in which (R_1 = *-methyl*), **8c** (R_2 = *-methyl*) and**8c** in which (R_3 = *-methyl*) exhibit less antitubercular activity as compared rifampicin against *M. bovis BCG* strain with IC_{90} values 30 > µg/mL. Introduction of methoxy group in aryl ring compound **8e** (R_1 = *-methoxy*) and **8f** (R_2 = *-methoxy*) displays less active against *M. bovis BCG* strain with IC_{90} value > 30 µg/mL as compared to standard rifampicin drug. Surprisingly, methoxy group at para position in compound **8g** (R_3 = *-methoxy*) exhibit excellent anti-mycobacterial activity against *M. bovis BCG* strain with IC_{90} value 2.70 µg/mL compared to rifampicin drug. Introduction of chloro group in aryl ring compound **8h** (R_1 = *-chloro*) and **8j** (R_3 = *-chloro*) displays promising antitubercular activity against *M. bovis BCG* strain with IC_{90} value 2.05 and 1.20 µg/mL, respectively.

When chloro group R_2 position in compound **8i** (R_2 = *-chloro*) are less active against *M. bovis BCG* strain with IC_{90} value > 30 µg/mL. When nitro group present at ortho position **8k** (R_2 = *-NO_2*) does not show any antitubercular activity against the *M. bovis BCG* strain. In compounds **8l** (R_3 = *-NO_2*) is highly potent against the *M. bovis BCG* strain with 1.24 µg/mL compared with rifampicin as a standard. Hence, among all the synthesized compounds **(8a–l)**, compounds **8g**, **8**, **8j** and **8 l**, displays promising anti-mycobacterial activity against *M. bovis BCG* and the results are summarized in Table 2.

Further, we screened the antitubercular activity against the *MTB* strain. From the 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates series **(8a–l)**, compound **8a** without any substituent on aryl ring showed lower anti-mycobacterial activity with IC_{90} value > 30 µg/mL against *MTB* strain as compared to rifampicin as a reference and the results are shown in Table 2. Compounds **8b** in which (R_1 = *-methyl*), **8c** (R_2 = *-methyl*) and **8d** in which (R_3 = *-methyl*) exhibits less active against *MTB* strain with IC_{90} values 30 > µg/mL. It is observed that *methoxy* group in compound **8e** (R_1 = *-methoxy*) and **8f** (R_2 = *-methoxy*) exhibit lesser activity against *MTB* strain with IC_{90} value that is > 30 µg/mL as compared with rifampicin drug. In compound **8g** (R_3 = *-methoxy*) exhibit promising tubercular

Table 2 Anti-mycobacterial activity of the 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates

Entry	Structures	*M. bovis BCG*		*MTB H37Ra*	
		IC_{50}	IC_{90}	IC_{50}	IC_{90}
8a		>30	>30	>30	>30
8b		>30	>30	>30	>30
8c		>30	>30	>30	>30
8d		>30	>30	>30	>30
8e		>30	>30	>30	>30
8f		>30	>30	>30	>30
8 g		0.18	2.70	0.49	2.65
8 h		0.15	2.05	0.72	2.35
8i		>30	>30	>30	>30
8j		0.45	1.20	0.68	2.04
8 k		>30	>30	>30	>30
8 l		0.29	1.24	1.16	2.41
[a]RP	–	0.0043 ± 0.00028	0.0173 ± 0.039	0.0019 ± 0.00022	0.020 ± 0.0021

IC_{50}/IC_{90} in µg/mL. Anti-mycobacterial activity of each agent was determined by serial dose-dependent dilutions

[a]Rifampicin as a standard reference antitubercular drugs and positive controls

activity against *MTB* strain with IC_{90} value that is 2.65 µg/mL as compared with rifampicin drug.

Introduction of chloro group in aryl ring compound **8h** (R_1 = *-chloro*) and **8j** (R_3 = *-chloro*) are highly potent against *MTB* strain with IC_{90} value 2.35 and 2.04 µg/mL, respectively. When chloro group R_2 position in compound **8i** (R_3 = *-chloro*) decreasing in antitubercular activity against *MTB* strain with IC_{90} value > 30 µg/mL compared to rifampicin drug. Replacing the chloro group by nitro group **8k** (R_2 = *-nitro*) exhibits lower activity with IC_{90}

Table 3 *In vitro* cytotoxicity of selected 2,4 thiazolidinedione conjugates

Entry	MCF-7 (Breast) Cell line		HCT 116 (Colorectal) Cell line		A549 (Lung) Cell line	
	GI_{50} (μg/mL)	GI_{90} (μg/mL)	GI_{50} (μg/mL)	GI_{90} (μg/mL)	GI_{50} (μg/mL)	GI_{90} (μg/mL)
8g	>100	>100	>100	>100	>100	>100
8h	>100	>100	>100	>100	>100	>100
8j	>100	>100	>100	>100	>100	>100
8l	>100	>100	>100	>100	>100	>100
Paclitaxel	0.0048	0.075	0.1279	5.715	0.0035	0.0706
Rifampicin	>100	>100	>100	>100	>100	>100

Table 4 Selectivity index against dormant *M. bovis BCG* and *MTB*

Entry	MCF-7		HCT 116		A549	
	H37Ra	BCG	H37Ra	BCG	H37Ra	BCG
8g	38	38	38	38	38	38
8h	41	47	41	47	41	41
8j	48	83	48	83	48	83
8l	40	80	40	80	40	80
Rifampicin	196	222	196	222	196	222

value > 30 μg/mL against *MTB* strain. Introduction of nitro group at para position **8l** (R_3 = *-nitro*) exhibits promising anti-mycobacterial activity with IC_{90} value 2.41 μg/mL against *MTB* strain. Hence, among all the synthesized compounds **8a–l**, compounds **8 g, 8h, 8j** and **8l** showed excellent antitubercular activity against *MTB* and the results are disclosed in Table 2.

Cytotoxicity

Highly active 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates **8g**, **8h**, **8j** and **8l** were further screened against different human cancer cells (MCF-7, HCT 116 and A549) to determine their toxicity (Table 3) [64]. The cytotoxicity results of these compounds indicate they are highly potent and specific inhibitors against *M. bovis BCG* and *MTB* strain with GI_{50}/GI_{90} (> 100 μg/mL).Thus, all the most active compounds were relatively non-toxic against MCF-7, HCT 116 and A549 cell lines with (GI_{50}/GI_{90}) of > 100.

Selectivity index

Selectivity index indicates that the highly potent compound is only active against *mycobacteria* but it is non-toxic against host human cell lines. Compound **8g**, **8h**, **8j** and **8l** showed very high SI, which is a good inhibitor of *M. bovis BCG* strain and results are described in Table 4.

The compound **8g**, **8h**, **8j** and **8l** showed very higher selectivity index, which is actually good inhibitor of *MTB* strain and detail study are shown in Table 4. According to a study on the drug susceptibility of TB, antitubercular activity was considered to be specific when the selectivity index was > 10 [65]. This study suggested that, compounds **8g**, **8h**, **8j** and **8l** display highest selectivity index > 10, suggesting that these compounds act as a highly potent anti-mycobacterial agent, and thus they should be modification for next level.

Table 5 Antibacterial activity IC_{90} (μg/mL)

Entry	*P. flurescense*	*E. coli*	*B. subtillus*	*S. aureus*
8g	>100	>100	>100	>100
8h	>100	>100	>100	>100
8j	>100	>100	>100	>100
8l	>100	>100	>100	>100
Ampicillin	4.36	1.46	10.32	1
Kanamycin	0.49	1.62	1.35	>30

Antibacterial activity

To determine the specificity of most potent compounds **8g**, **8h**, **8j** and **8l** were evaluated for their antibacterial activity against four bacteria strains (Gram-negative strains: *P. flurescense*, *E. coli*, Gram-positive strains: *B. subtillus, S. aureus*). All the active compounds exhibited higher specificity toward *MTB*, *BCG* strains and it is inactive against bacterial strains and detailed study is described in Table 5.

Experimental

Methods and material

All reagents were purchased from Merck and Spectrochem used without further purification. Melting points of all the synthesized compounds were determined in open capillary tube and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX-400 MHz NMR spectrometer and ^{13}C NMR spectra were recorded on a Bruker DRX-100 MHz NMR in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard and chemical shifts are in δ ppm. High-resolution mass spectra (HRMS) were recorded on Agilent 6520 (QTOF) ESI-HRMS instrument. The purity of each of the compound was checked by thin-layer chromatography (TLC) using silica gel, ($60F_{254}$) and visualization was accomplished by iodine/ultraviolet light.

Typical experimental procedure for the synthesis of 4-(prop-2-yn-1-yloxy)benzaldehyde (2)

To the stirred solution of appropriate 4-hydroxybenzaldehyde **1** (20 mmol) in *N,N*-dimethylformamide (DMF) (20 mL), K_2CO_3 (24 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, which results into the oxyanion. To this mixture, propargyl bromide (20 mmol) was added and stirred for 4 h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction was quenched by crushed ice and extracted in ethyl acetate (20 mL × 3). The combined organic layers wash with brine solution (2 × 15 mL) and dried over $NaSO_4$. The solvent was removed under reduced pressure and used for the further reaction without purification.

General experimental procedure for the synthesis of 5-(4 (ethynyloxy)benzylidene)thiazolidine-2,4-dione (4)

A mixture of 4-(prop-2-yn-1-yloxy)benzaldehyde **2** (0.5 mmol), thiazolidine-2,4-dione **3** (0.5 mmol), and sodium acetate (0.5 mmol) were dissolved in glacial acetic acid (5 mL) and were reflux at 100 °C for 5 h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction was quenched by crushed ice and extracted in ethyl acetate (20 mL × 3). The combined organic layers wash with brine solution (2 × 15 mL) and dried over $NaSO_4$. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure and used for the further reaction without purification.

General experimental procedure for the synthesis of substituted 2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl) phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (8a–l)

To the stirred solution of 5-(4-(ethynyloxy)benzylidene) thiazolidine-2,4-dione **4** (0.5 mmol), substituted 2-Azido-*N*-phenylacetamides **7a–l** (0.5 mmol) and copper diacetate $(CuOAc)_2$ (20 mol.%) in *t*-BuOH-H_2O (3:1, 8 mL) were added and the resulting mixture was stirred at room temperature for 20 h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (2 × 15 mL). The organic extracts were washed with brine solution (2 × 15 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford the corresponding crude compounds. The obtained crude compounds were recrystallized using DMF.

2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (8a)

Compound **8a** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7a** for 20 h.yellow solid; Mp: 214-216 °C; Yield: 89%; FT-IR (cm^{-1}): 3267 (N–H stretching), 1728 and 1635 (C=O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.62 (s, 1H, NH), 9.41 (s, 1H, NH), 8.30 (s, 1H, triazole), 7.97 (s, 1H, –CH=C), 7.72-7.69 (m, 2H, Ar–H), 7.61-7.58 (m, 2H, Ar–H), 7.40-7.38 (m, 2H, Ar–H), 7.17–7.16 (m, 1H, Ar–H), 7.06–6.99 (m, 3H, Ar–H), 5.36 (s, 2H, –OCH_2) and 5.30 (s, 2H, –NCH_2CO–); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.55, 166.90, 161.25, 160.29, 143.31, 135.96, 132.79, 130.93, 130.85, 129.84, 129.38, 127.55, 125.27, 124.16, 56.93 and 48.91; HRMS (ESI-qTOF): Calcd for $C_{21}H_{18}N_5O_4S$ $[M+H]^+$, 436.3442: found: 436.3420.

2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) methyl)-1H-1,2,3-triazol-1-yl)-N-(o-tolyl)acetamide (8b)

Compound **8b** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7b** for 20 h.yellow solid; Mp: 232–234 °C; Yield: 84%; FT-IR (cm^{-1}): 3250 (N–H stretching), 1732 and 1658 (C=O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.49 (s, 1H, NH), 9.40 (s, 1H, NH), 8.26 (s, 1H, triazole), 7.78 (s, 1H, –CH=C), 7.38–7.27 (m, 4H, Ar–H), 7.13–6.92 (m, 4H, Ar–H), 5.36 (s, 2H, –OCH_2), 5.17 (s, 2H, –NCH_2CO–) and 2.27 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 171.32, 168.33, 161.90, 160.38, 143.31, 139.79, 137.09, 135.01, 132.80, 130.94, 130.86, 129.67, 129.46, 127.49, 125.28, 124.20, 121.29, 57.85, 47.70 and 22.39; HRMS

(ESI-qTOF): Calcd for $C_{22}H_{20}N_5O_4S$ $[M+H]^+$, 450.3526: found: 450.3579.

4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) methyl)-1H-1,2,3-triazol-1-yl)-N-(m-tolyl)acetamide (8c)

Compound **8c** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7c** for 20 h.yellow solid; Mp: 240–242 °C; Yield: 82%; FT-IR (cm^{-1}): 3246 (N–H stretching), 1742 and 1636 (C = O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.42 (s, 1H, NH), 9.33 (s, 1H, NH), 8.31 (s, 1H, triazole), 7.83 (s, 1H, –CH = C), 7.54 (s, 1H, Ar–H), 7.54–7.42 (m, 2H, Ar–H), 7.37–7.34 (m, 2H, Ar–H), 7.23–7.19 (m, 2H, Ar–H), 6.91–6.89 (m, 1H, Ar–H), 5.35 (s, 2H, –OCH_2), 5.29 (s, 2H, –NCH_2CO–) and 2.27 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 171.35, 167.36, 161.89, 160.35, 143.91, 139.79, 136.15, 133.23, 129.67, 129.63, 129.47, 127.53, 125.80, 124.50, 124.20, 121.57, 115.74, 58.44, 48.91 and 22.10; HRMS (ESI-qTOF): Calcd for $C_{22}H_{20}N_5O_4S$ $[M+H]^+$, 450.3520: found: 450.3576.

2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) methyl)-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide (8d)

Compound **8d** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7d** for 20 h.yellow solid; Mp: 248–250 °C; Yield: 86%; FT-IR (cm^{-1}): 3254 (N–H stretching), 1696 and 1641 (C=O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.66 (s, 1H, NH), 9.47 (s, 1H, NH), 8.39 (s, 1H, triazole), 7.88 (s, 1H, –CH=C), 7.64–7.62 (m, 2H, Ar–H), 7.53-7.44 (m, 4H, Ar–H), 7.42–7.40 (m, 2H, Ar–H), 5.40 (s, 4H, –OCH_2, –NCH_2CO–) and 2.28 (s, 3H, –CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.56, 165.72, 131.20, 157.04, 144.94, 141.62, 139.87, 128.78, 128.29, 127.76, 124.38, 124.20, 124.07, 123.34, 118.80, 58.44, 48.92 and 21.76; HRMS (ESI-qTOF): Calcd for $C_{22}H_{20}N_5O_4S$ $[M+H]^+$, 450.3552: found: 450.3578.

2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) methyl)-1H-1,2,3-triazol-1-yl)-N-(2-methoxyphenyl)acetamide (8e)

Compound **8e** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7e** for 20 h. Pale yellow solid; Mp: 204–206 °C; Yield: 81%; FT-IR (cm^{-1}): 3275 (N–H stretching), 1738 and 1639 (C = O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.38 (s, 1H, NH), 9.53 (s, 1H, NH), 8.33 (s, 1H, triazole), 7.84 (s, 1H, –CH = C), 7.55–7.47 (m, 4H, Ar–H), 7.39–7.35 (m, 1H, Ar–H), 7.23-7.20 (m, 1H, Ar–H), 6.93-6.91 (m, 2H, Ar–H), 5.34 (s, 2H, –OCH_2), 5.31 (s, 2H, –NCH_2CO–) and 3.73 (s, 3H, -OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 170.47, 167.19, 161.96, 160.38, 143.33, 141.16, 138.80, 135.94, 132.27, 130.80, 129.46, 127.47, 125.43, 122.06, 119.79, 115.72, 59.28, 55.71 and 48.56; HRMS (ESI-qTOF): Calcd for $C_{22}H_{20}N_5O_5S$ $[M+H]^+$, 466.2638: found: 466.2695.

2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) methyl)-1H-1,2,3-triazol-1-yl)-N-(3-methoxyphenyl)acetamide (8f)

Compound **8f** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7f** for 20 h.for 20 h. yellow solid; Mp: 216-218 °C; Yield: 80%; FT-IR (cm^{-1}): 3205 (N–H stretching), 1701 and 1632 (C = O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.41 (s, 1H, NH), 9.47 (s, 1H, NH), 8.32 (s, 1H, triazole), 7.97 (s, 1H, –CH = C), 7.70 (s, 1H, Ar–H), 7.48–7.46 (m, 2H, Ar–H), 7.18–7.13 (m, 3H, Ar–H), 7.08-7.06 (m, 1H, Ar–H), 6.23-6.22 (m, 1H, Ar–H), 5.35 (s, 2H, –OCH_2), 5.31 (s, 2H, –NCH_2CO–) and 3.84 (s, 3H, -OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 168.68, 165.97, 162.06, 160.26, 143.91, 139.15, 135.94, 133.78, 131.72, 129.62, 129.37, 127.60, 125.78, 124.49, 121.56, 115.71, 58.98, 55.42 and 48.55; HRMS (ESI-qTOF): Calcd for $C_{22}H_{20}N_5O_5S$ $[M+H]^+$, 466.3125: found:466.3167.

2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy) methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl)acetamide (8g)

Compound **8g** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7g** for 20 h. Pale yellow solid; Mp: 226–228 °C; Yield: 82%; FT-IR (cm^{-1}): 3165 (N–H stretching), 1701 and 1614 (C = O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.34 (s, 1H, NH), 9.55 (s, 1H, NH), 8.31 (s, 1H, triazole), 7.88 (s, 1H, –CH = C), 7.58–7.49 (s, 3H, Ar–H), 7.28–7.19 (m, 5H, Ar–H), 5.17 (s, 2H, –OCH_2) and5.11 (s, 2H, –NCH_2CO–); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.83, 167.48, 161.96, 160.36, 141.16, 138.59, 136.15, 133.53, 129.63, 127.50, 125.79, 124.50, 122.06, 115.74, 58.13, 55.13 and 49.19; HRMS (ESI-qTOF): Calcd for $C_{22}H_{20}N_5O_5S$ $[M+H]^+$, 466.3762: found: 466.3736.

N-(2-chlorophenyl)-2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (8h)

Compound **8h** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7h** for 20 h. Yellow solid; Mp: 228–230 °C; Yield: 80%; FT-IR (cm^{-1}): 3271 (N–H stretching), 1740 and 1620 (C=O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.56 (s, 1H, NH), 9.34 (s, 1H,

NH), 8.25 (s, 1H, triazole), 7.91 (s, 1H, –CH = C), 7.82–7.78 (m, 1H, Ar–H), 7.72–7.64 (m, 1H, Ar–H), 7.50–7.22 (m, 6H, Ar–H), 5.34 (s, 2H, $–OCH_2$) and 5.31 (s, 2H, $–NCH_2CO–$); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.28, 165.76, 160.90, 157.34, 142.47, 139.90, 136.65, 134.01, 132.30, 130.38, 128.27, 127.80, 124.07, 123.89, 123.41, 123.04, 118.84, 56.65 and 49.79; HRMS (ESI-qTOF): Calcd for $C_{21}H_{17}ClN_5O_4S$ $[M+H]^+$, 470.3252: found: 470.3287.

N-(3-chlorophenyl)-2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (8i)

Compound **8i** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7i** for 20 h. Yellow solid; Mp: 246–248 °C; Yield: 78%; FT-IR (cm^{-1}): 3273 (N–H stretching), 1740 and 1618 (C = O stretching); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 9.89 (s, 1H, NH), 9.21 (s, 1H, NH), 8.12 (s, 1H, triazole), 7.91 (s, 1H, –CH=C), 7.73 (s, 1H, Ar–H), 7.55–7.48 (m, 2H, Ar–H), 7.33–7.31 (m, 1H, Ar–H), 7.16-7.12 (m, 1H, Ar–H), 7.04–6.97 (m, 2H, Ar–H), 6.86–6.84 (m, 1H, Ar–H), 5.28 (s, 2H, $–OCH_2$) and 5.11 (s, 2H, $–NCH_2CO–$); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 170.76, 165.92, 160.88, 156.76, 141.14, 139.83, 136.79, 133.23, 130.79, 128.40, 127.87, 125.62, 124.22, 123.49, 122.19, 120.59, 118.71, 56.91 and 48.54; HRMS (ESI-qTOF): Calcd for $C_{21}H_{17}ClN_5O_4S$ $[M+H]^+$, 470.3248: found: 470.3288.

N-(4-chlorophenyl)-2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (8j)

Compound **8j** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7j** for 20 h. Yellow solid; Mp: 250–252 °C; Yield: 84%; FT-IR (cm^{-1}): 3254 (N–H stretching), 1702 and 1647 (C=O stretching); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 10.11 (s, 1H, NH), 9.43 (s, 1H, NH), 8.32 (s, 1H, triazole), 7.82 (s, 1H, –CH = C), 7.53–7.45 (m, 4H, Ar–H), 7.37–0.32 (m, 2H, Ar–H), 7.24–7.19 (m, 2H, Ar–H), 5.48 (s, 2H, $–OCH_2$) and 5.29 (s, 2H, $–NCH_2CO–$); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 168.06, 165.70, 161.74, 156.47, 144.59, 139.58, 130.15, 130.06, 128.20, 127.77, 124.00, 123.35, 118.90, 116.34, 116.12, 58.41 and 48.91; HRMS (ESI-qTOF): Calcd for $C_{21}H_{17}ClN_5O_4S$ $[M+H]^+$, 470.3272: found: 470.3284.

2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-nitrophenyl)acetamide (8k)

Compound **8 k** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7 k** for 20 h. Brown solid; Mp: 242–244 °C; Yield: 74%; FT-IR (cm^{-1}): 3170 (N–H stretching), 1709 and 1642 (C=O stretching); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 10.69 (s, 1H, NH), 9.38 (s, 1H, NH), 8.32 (s, 1H, triazole), 7.95 (s, 1H, –CH = C), 7.77 (s, 1H, Ar–H), 7.71–7.68 (m, 1H, Ar–H), 7.46–7.43 (m, 1H, Ar–H), 7.39–7.35 (m, 1H, Ar–H), 7.17–7.14 (m, 2H, Ar–H), 7.07–7.04 (m, 2H, Ar–H), 5.39 (s, 2H, $–OCH_2$) and 5.31 (s, 2H, $–NCH_2CO–$); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 169.89, 165.87, 161.25, 157.03, 148.53, 140.91, 137.71, 136.49, 134.25, 131.40, 130.30, 129.19, 128.18, 127.19, 127.09, 126.88, 56.11 and 49.94; HRMS (ESI-qTOF): Calcd for $C_{21}H_{17}N_6O_6S$ $[M+H]^+$, 481.2836: found: 481.2852.

2-(4-((4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-nitrophenyl)acetamide (8l)

Compound **8l** was obtained via 1,3-dipolar cycloaddition reaction between alkyne **4** and azide **7l** for 20 h. Brown solid; Mp: 254–256 °C; Yield: 72%; FT-IR (cm^{-1}): 3042 (N–H stretching), 1743 and 1687 (C=O stretching); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 10.08 (s, 1H, NH), 9.55 (s, 1H, NH), 8.53 (s, 1H, triazole), 7.70 (s, 1H, –CH = C), 7.51–7.47 (m, 2H, Ar–H), 7.28–7.01 (m, 4H, Ar–H), 6.99–6.81 (m, 2H, Ar–H) and 5.00 (s, 2H, $–OCH_2$, $–NCH_2CO–$); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 172.06, 169.19, 161.75, 157.85, 150.43, 143.01, 140.08, 139.47, 136.47, 133.02, 130.33, 129.08, 127.53, 127.39, 57.48 and 48.73; HRMS (ESI-qTOF): Calcd for $C_{21}H_{17}N_6O_6S$ $[M+H]^+$, 481.2876: found: 481.2848.

Conclusions

Synthesis of 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates (**8a**–**l**) and their antitubercular activity against *M. Bovis BCG* and *MTB* strain has been reported. Four compounds **8g**, **8h**, **8j** and **8l** of the series exhibited good to excellent activity against *M. bovis BCG* with IC_{90} range 1.20–2.70 and *MTB H37Ra* with IC_{90} range 1.24–2.65 µg/mL, respectively. Most potent compounds displayed low cytotoxicity against MCF-7, HCT 116 and A549 cell line using MTT assay, suggest that these molecules possess highly pharmacodynamic properties. Most of the active compounds **8g**, **8h**, **8j** and **8l** exhibit high selectivity index > 10 against MCF-7, HCT 116 and A549 which indicated that they act as a prominent antitubercular agent. All these results suggest that the potential and significance of emergent novel 1,2,3-triazoles-incorporated 2,4 thiazolidinedione conjugates to treat mycobacterial infections.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest, financial or otherwise.

References

1. C. Dye, B.G. Williams, Science **328**, 856 (2010)
2. WHO Global Tuberculosis Report 2014; World Health Organization: Geneva, 2014; http://www.who.int/tb/publications/ global report/en/
3. S. Loewenberg, Lancet **379**, 205 (2012)
4. A.I. Zumla, S.H. Gillespie, M. Hoelscher, P.P. Philips, S.T. Cole, I. Abubakar, T.D. McHugh, M. Schito, M. Maeurer, A.J. Nunn, Lancet Infect. Dis. **4**, 327 (2014)
5. CDC, 2011, MMWR Morb Mortal Wkly Rep. 61, 883 (2012)
6. R.J. Rees, Br. Med. Bull. **25**, 183 (1969)
7. Z.F. Udwadia, R.A. Amale, K.K. Ajbani, C. Rodrigues, Clin. Infect. Dis. **54**, 579 (2012)
8. M.S. Butler, M.A. Blaskovich, M.A. Cooper, J Antibiot (Tokyo) **66**, 571 (2013)
9. A.H. Diacon, P.R. Donald, A. Pym, M. Grobusch, R.F. Patientia, R. Mahanyele, N. Bantubani, R. Narasimooloo, T. De Marez, R. van Heeswijk, Antimicrob. Agents Chemother. **6**, 3271 (2012)
10. A. Massarotti, S. Aprile, V. Mercalli, E.D. Grosso, G. Grosa, G. Sorba, G.C. Tron, Chem. Med. Chem. **9**, 2497 (2014)
11. K.D. Hanni, D.A. Leigh, Chem. Soc. Rev. **39**, 1240 (2010)
12. K. Kempe, A. Krieg, C.R. Becer, U.S. Schubert, Chem. Soc. Rev. **41**, 176 (2012)
13. A.D. Moorhouse, J.E. Moses, Chem. Med. Chem. **3**, 715 (2008)
14. R.D. Simone, M.G. Chini, I. Bruno, R. Riccio, D. Mueller, O. Werz, G. Bifulco, J. Med. Chem. **54**, 1565 (2011)
15. B. Zhang, Eur. J. Med. Chem. **168**, 357 (2019)
16. N. Fu, S. Wang, Y. Zhang, C. Zhang, D. Yang, L. Weng, B. Zhao, L. Wang, Eur. J. Med. Chem. **136**, 596 (2017)
17. S.G. Agalave, S.R. Maujan, V.S. Pore, Chem. Asian J. **6**, 2696 (2011)
18. S. Hakimian, A. Cheng-Hakimian, G.D. Anderson, J.W. Miller, Expert Opin. Pharmacother. **8**, 1931 (2007)
19. S. Zhang, Z. Xu, C. Gao, Q.C. Ren, L. Chang, Z.S. Lv, L.S. Feng, Eur. J. Med. Chem. **138**, 501 (2017)
20. N. Boechat, V.F. Ferreira, S.B. Ferreira, M.L.G. Ferreira, F.C. da Silva, M.M. Bastos, M.S. Costa, M.C.S. Lourenço, 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. **54**, 5988 (2011)
21. C. Menendez, S. Gau, C. Lherbet, F. Rodriguez, C. Inard, M.R. Pasca, M. Baltas, Eur. J. Med. Chem. **46**, 5524 (2011)
22. 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. 55, 3911 (2012)
23. Y. Tian, Z. Liu, J. Liu, B. Huang, D. Kang, H. Zhang, E.D. Clercq, D.D. Mans, C. Pannecouque, K.H. Lee, C.H. Chen, P. Zhan, X. Liu, Eur. J. Med. Chem. **151**, 339 (2018)
24. M. Allam, A.K.D. Bhavani, A. Mudiraj, N. Ranjan, M. Thippana, P.P. Babu, Eur. J. Med. Chem. **156**, 43 (2018)
25. Y. Chinthala, A. Kumar, A.D. Sarfaraz, S.P. Singh, N.K. Arigari, N. Gupta, S.K.V.N. Satya, J.K. Kumar, F. Khan, A.K. Tiwari, G. Paramjit, Eur. J. Med. Chem. **70**, 308 (2013)
26. S. Rekha, U. Shantharam, V. Chandy, Int. Res. J. Pharm. **2**, 81 (2011)
27. J. Sindhu, H. Singh, J.M. Khurana, C. Sharma, K.R. Aneja, Chin. Chem. Lett. **26**, 50 (2015)
28. S. Ponnuchamy, S. Kanchithalaivan, R.R. Kumar, M.A. Ali, T.S. Choon, Bioorg. Med. Chem. Lett. **24**, 1089 (2014)
29. D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, C.W. Day, D.F. Smee, P. Grellier, R. Lesyk, Eur. J. Med. Chem. **66**, 228 (2013)
30. B.R. Bhattarai, B. Kafle, J.S. Hwang, S.W. Ham, K.H. Lee, H. Park, I.O. Han, H. Cho, Bioorg. Med. Chem. Lett. **20**, 6758 (2010)
31. X. Li, R.K. Russell, J. Spink, S. Ballentine, C. Teleha, S. Branum, K. Wells, D. Beauchamp, R. Patch, H. Huang, M. Player, W. Murray, Org. Process Res. Dev. **18**, 321 (2014)
32. A.M. Ali, G.E. Saber, N.M. Mahfouz, M.A. El-Gendy, A.A. Radwan, M.A. Hamid, Arch. Pharm. Res. **30**, 1186 (2007)
33. L.A. Dakin, M.H. Block, H. Chen, E. Code, J.E. Dowling, X. Feng, A.D. Ferguson, I. Green, A.W. Hird, T. Howard, E.K. Keeton, M.L. Lamb, P.D. Lyne, H. Pollard, J. Read, A.J. Wu, T. Zhang, X. Zheng, Bioorg. Med. Chem. Lett. **22**, 4599 (2012)
34. D.O. Bozdag, E.J. Verspohl, E.N. Das, R.M. Kaup, K. Bauer, M. Sarıkaya, B. Evranos, R. Ertan, Bioorg. Med. Chem. **16**, 6747 (2008)
35. A.K.M. Iqbal, A.Y. Khan, M.B. Kalashetti, N.S. Belavagi, Y.D. Gong, I.A.M. Khazi, Eur. J. Med. Chem. **53**, 308 (2012)
36. N. Zidar, T. Tomasic, R. Sink, A. Kovac, D. Patin, D. Blanot, C. Contreras- Martel, A. Dessen, M. M. Premru, A. Zega, S. Gobec, L. P. Masic, D. Kikelj, Eur. J. Med. Chem. 46, 5512 (2011)
37. F. W. Barros, T. G. Silva, M. G. da Rocha Pitta, D. P.Bezerra, L. V. Costa-Lotufo, M. O. de Moraes, C. Pessoa, M. A. de Moura, F. C. de Abreu, C. de Lima Mdo, S. L. Galdino, R. Pitta Ida, M. O. Goulart, Bioorg. Med. Chem., 20, 3533 (2012)
38. Z. Xia, C. Knaak, J. Ma, Z.M. Beharry, C. McInnes, W. Wang, A.S. Kraft, C.D. Smith, J. Med. Chem. **52**, 74 (2009)
39. F.H.A. Leite, P.B.G.S. Santiago, T.Q. Froes, J.S. Filho, S.G. Silva, R.M. Ximenes, A.R. Faria, D.J. Brondani, J.F.C. Albuquerque, M.S. Castilho, Eur. J. Med. Chem. **123**, 639 (2016)
40. K. Liu, W. Rao, H. Li, Q. Parikh, T.L. Guo, S. Grant, G.E. Kellogg, S. Zhang, Eur. J. Med. Chem. **47**, 125 (2012)
41. A. Maleki, A. Sarvary, RSC Adv. **5**, 60938 (2015)
42. A. Maleki, V. Eskandarpour, Jour. of Iran. Chem. Soc. **16**, 1459 (2019)
43. A.T. Kal-Koshvandi, M.R. Ahghari, A. Maleki, New J. Chem. **44**, 12619 (2020)
44. A. Maleki, M. Panahzadeh, R. Eivazzadeh-keihan, Green Chem. Lett and Rev. **12**, 395 (2019)
45. A.A. Ali, M. Konwar, M. Chetia, D. Sarma, Tetrahedron Lett. **57**, 5661 (2016)
46. M. Tavassoli, A.L. Isfahani, M. Moghadam, S. Tangestaninejad, V. Mirkhani, I.M. Baltork, ACS Sustainable Chem. Eng. **4**, 1454 (2016)
47. M. Dabiri, S.K. Movahed, D.I. MaGee, Res. Chem. Intermed. **41**, 3335 (2015)
48. H. Singh, J. Sindhu, J.M. Khurana, C. Sharma, K.R. Aneja, Eur. J. Med. Chem. **77**, 145 (2014)
49. A.Z. Ahmady, F. Heidarizadeh, M. Keshavarz, Synth. Commun. **43**, 2100 (2013)
50. A. Marra, A. Vecchi, C. Chiappe, B. Melai, A. Dondoni, J. Org. Chem. **73**, 2458 (2008)
51. Y.B. Zhao, Z.Y. Yan, Y.M. Liang, Tetrahedron Lett. **47**, 1545 (2006)
52. G. Wang, Z. Peng, J. Wang, X. Li, J. Li, Eur. J. Med. Chem. **125**, 423 (2017)
53. C. Ferroni, A. Pepe, Y. Sang Kim, S. Lee, A. Guerrini, M. D. Parenti, A. Tesei, A. Zamagni, M. Cortesi, N. Zaffaroni, M. De Cesare, G. L. Beretta, J. B. Trepel, S. V. Malhotra, G. Varchi, J. Med. Chem. 60, 3082 (2017)
54. K.C. Tiew, D. Dou, T. Teramoto, Bioorg. Med. Chem. **20**, 1213 (2012)
55. V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, Angew. Chem. Int. Ed. **41**, 2596 (2002)

56. J. Sultana, N.D. Khupse, S. Chakrabarti, P. Chattopadhyay, D. Sarma, Tetrahedron Lett. **60**, 1117 (2019)
57. Z. Zhang, Q. Zhou, F. Ye, Y. Xia, G. Wu, M.L. Hossain, Y. Zhang, J. Wang, Adv. Synth. Catal. **357**, 2277 (2015)
58. D. Gangaprasad, J. Paul Raj, T. Kiranmye, K. Karthikeyan, J. Elangovan, European J. Org. Chem. 2016, 5642 (2016)
59. Y.Y. Xie, Y.C. Wang, Y. He, D.C. Hu, H.S. Wang, Y.M. Pan, Green Chem. **19**, 656 (2017)
60. I. Proietti Silvestri, F. Andemarian, G. N. Khairallah, S. Wan Yap, T. Quach, S. Tsegay, C. M. Williams, R. A. J. O'Hair, P. S. Donnelly, S. J. Williams, Org. Biomol. Chem. 9, 6082 (2011)
61. W.S. Brotherton, R.J. Clark, L. Zhu, J. Org. Chem. **77**, 6443 (2012)
62. K. Yamamoto, T. Bruun, J.Y. Kim, L. Zhang, M. Lautens, Org. Lett. **18**, 2644 (2016)
63. I. E. Pardini, M. Gagliardi, M. C. Colone, M. Stringaro, A. R. Teloni, R. Brunori, L. Nisini, R. Fattorini, L. Giannoni, F. Microbes Infect. 14, 959 (2012) and references cited therin
64. A. A. Van de Loosdrecht, R. H. Beelen, G. J. Ossenkoppele, M. G. Broekhoven, M. M, Langenhuijsen, J. Immunol. Methods, 17, 311 (1994)
65. R.C. Hartkoorn, B. Chandler, A. Owen, S.A. Ward, S.B. Squire, D.J. Back, S.H. Khoo, Tuberculosis **87**, 248 (2007)