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

Original Paper Published: 19 January 2021

Volume 18, pages 2035–2046, (2021) Cite this article

Journal of the Iranian Chemical Society

Aims and scope

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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.

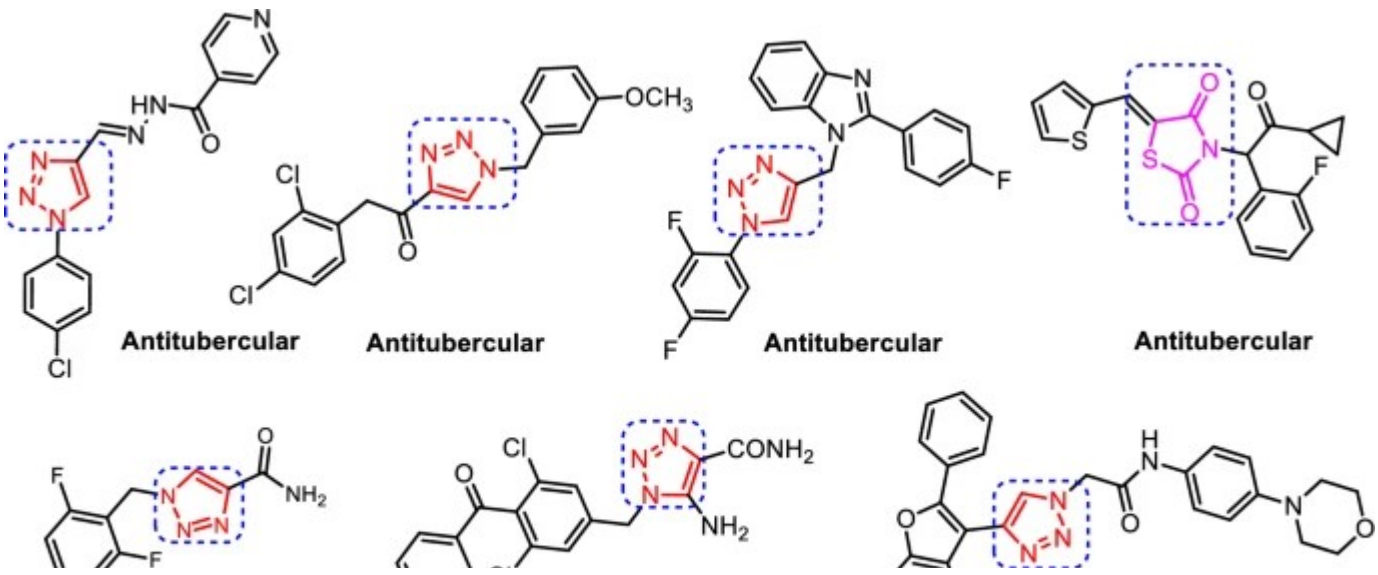
Introduction

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 [19,20,21,22], anti-HIV [23] and anticancer [24]. Some molecular structures of antitubercular agents bearing 1,2,3-triazolyl scaffolds are shown in Fig. 1.

Fig. 1

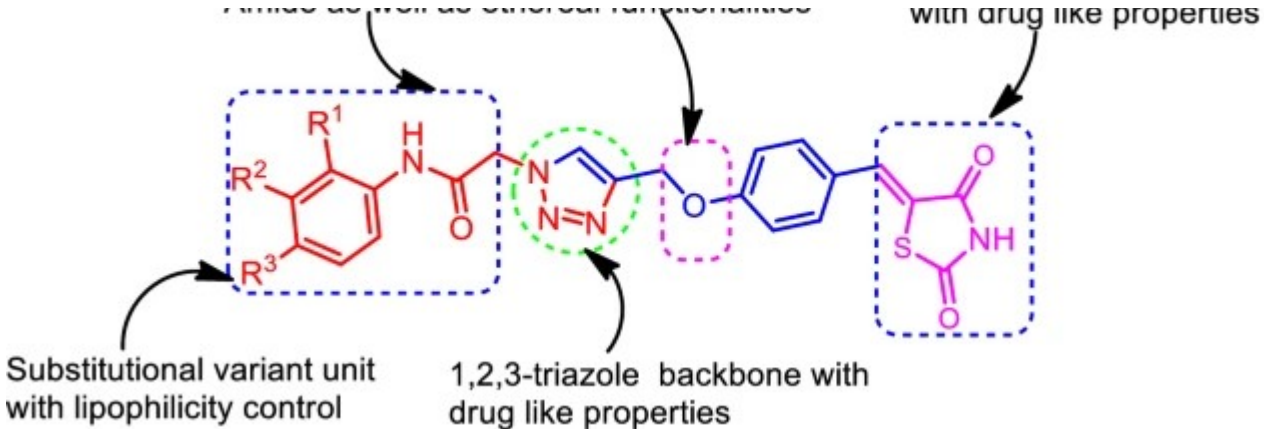


1,2,3-triazole-incorporated bioactive molecules

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 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.

Fig. 2



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

Considering the therapeutic significance of the above, herein, we have planned and synthesized 1,2,3-triazolesbearing 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.

Results and discussion

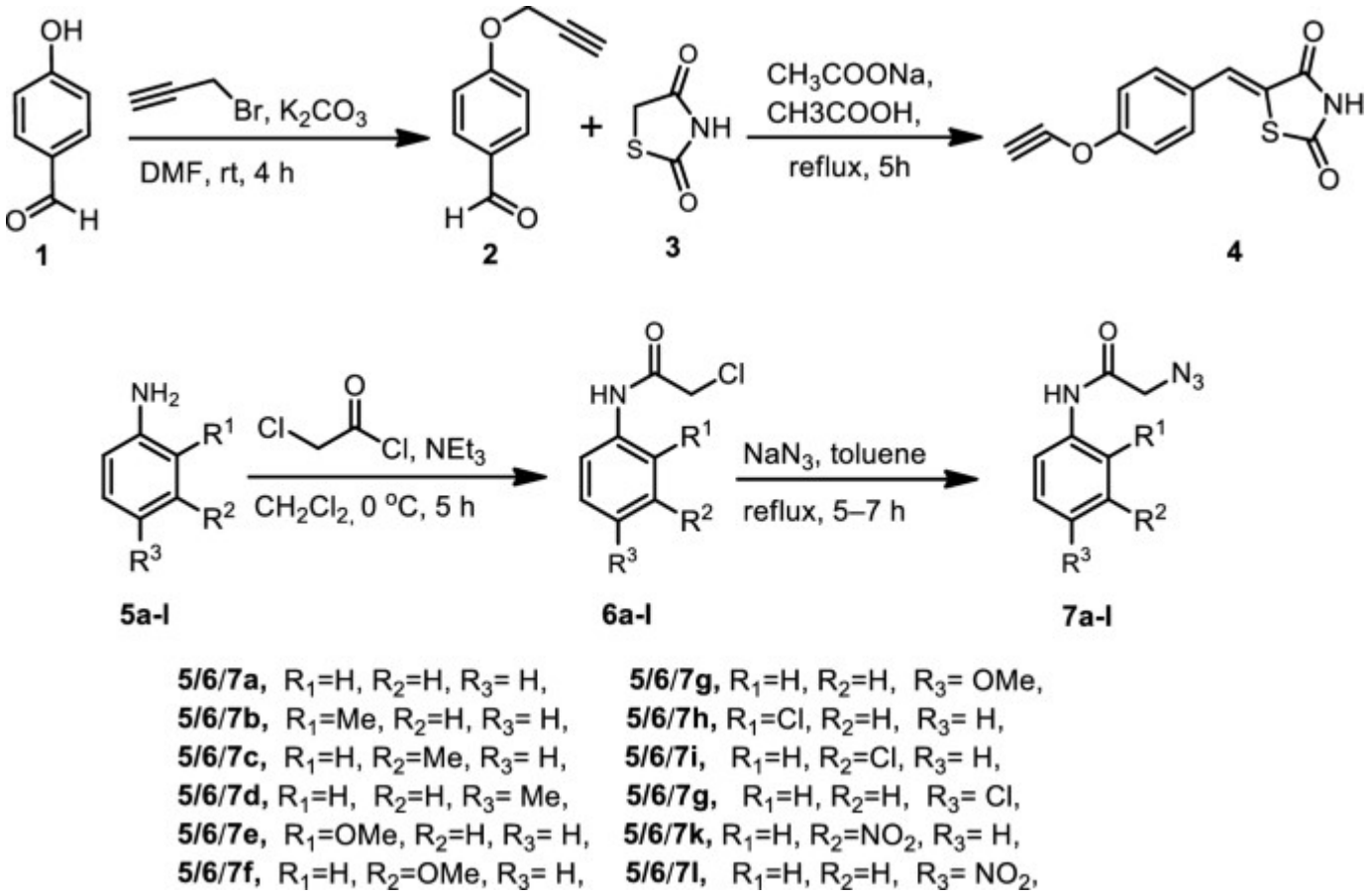
Chemistry

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)benzaldehyde2 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] 7a–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).

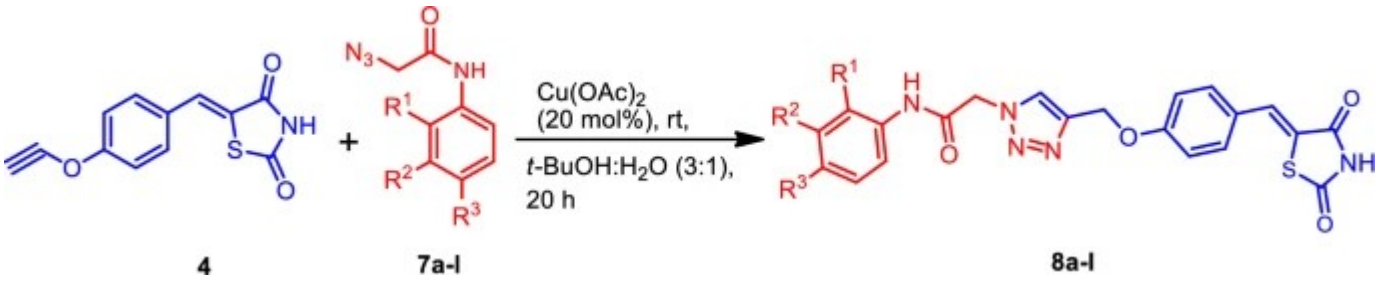
Scheme 1



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

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.

Scheme 2



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

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).

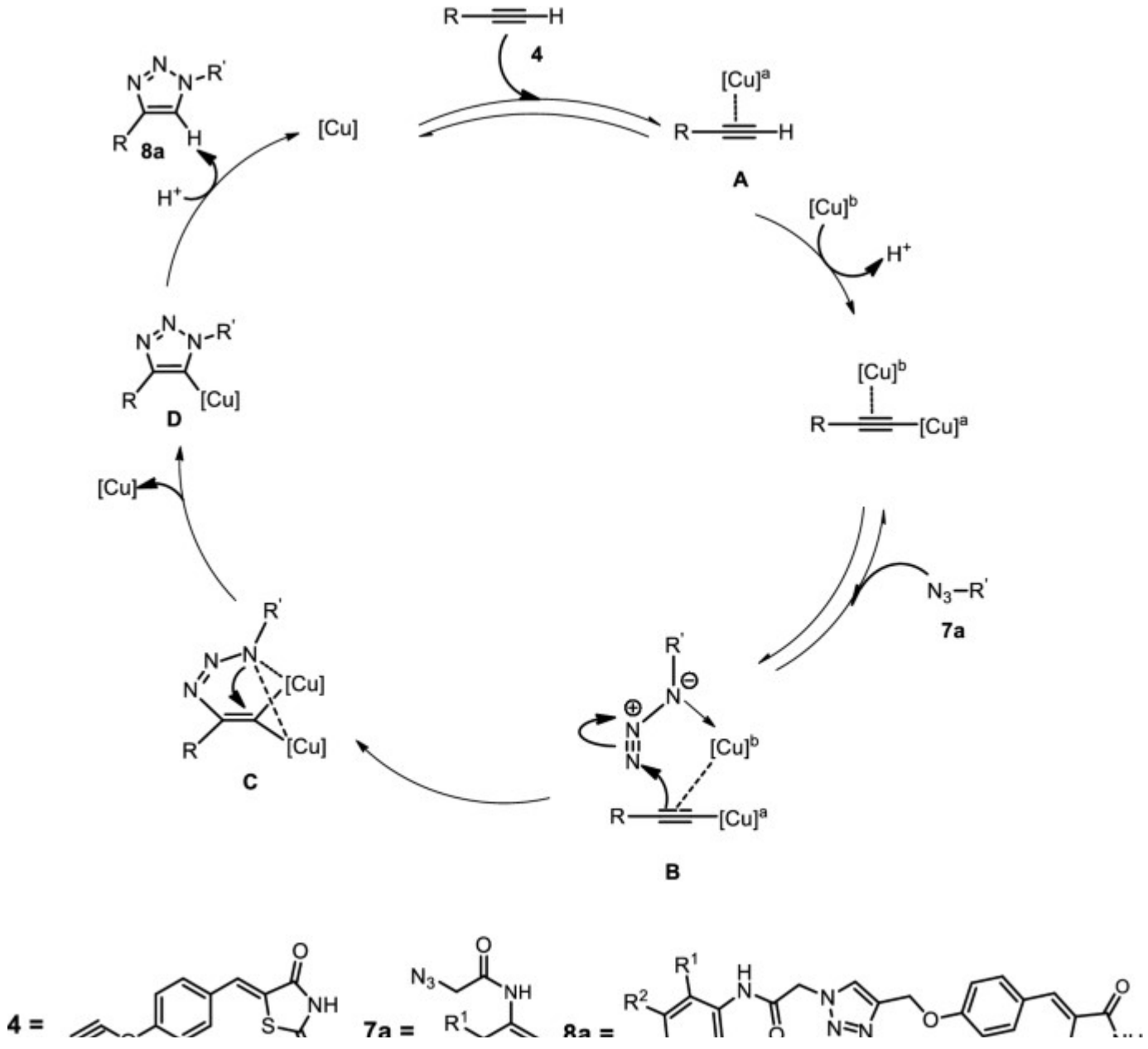
Table 1 Comparative catalytic performance of the $Cu(OAc)_2$ with other previously reported catalysts

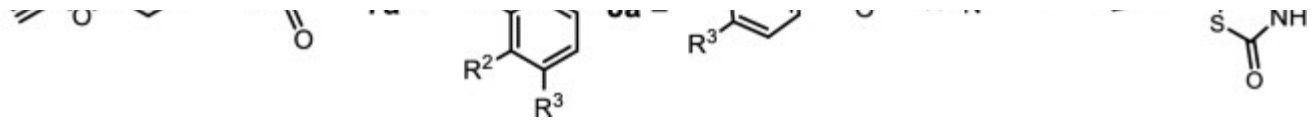
All the newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS techniques. In the ^{1}H NMR spectra of representative compound 8a displays two sharp singlet at δ 5.30 and 5.36 ppm as a methylene protons of $-CH_2-CO-$ and $-CH_2-O-$, respectively. The singlet peak appeared at 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).

Fig. 3





Plausible mechanisms for the CuAAC reaction

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.

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

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, 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*) and8c 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 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} 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.

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

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.

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

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.

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.

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

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); ^{1}H 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); ^{1}H 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); ^{1}H 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); ^{1}H 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.

References

1. C. Dye, B.G. Williams, Science 328, 856 (2010)

Article CAS PubMed Google Scholar

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)

Article PubMed Google Scholar

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)

Article Google Scholar

5. CDC, 2011, MMWR Morb Mortal Wkly Rep. 61, 883 (2012)

6. R.J. Rees, Br. Med. Bull. 25, 183 (1969)

Article CAS PubMed Google Scholar

7. Z.F. Udwadia, R.A. Amale, K.K. Ajbani, C. Rodrigues, Clin. Infect. Dis. 54, 579 (2012)

Article PubMed Google Scholar

8. M.S. Butler, M.A. Blaskovich, M.A. Cooper, J Antibiot (Tokyo) 66, 571 (2013)

Article CAS Google Scholar

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)

Article Google Scholar

10. A. Massarotti, S. Aprile, V. Mercalli, E.D. Grosso, G. Grosa, G. Sorba, G.C. Tron, Chem. Med. Chem. 9, 2497 (2014)

Article CAS PubMed Google Scholar

11. K.D. Hanni, D.A. Leigh, Chem. Soc. Rev. 39, 1240 (2010)

Article PubMed Google Scholar

12. K. Kempe, A. Krieg, C.R. Becer, U.S. Schubert, Chem. Soc. Rev. 41, 176 (2012)

Article CAS PubMed Google Scholar

13. A.D. Moorhouse, J.E. Moses, Chem. Med. Chem. 3, 715 (2008)

Article CAS PubMed Google Scholar

14. R.D. Simone, M.G. Chini, I. Bruno, R. Riccio, D. Mueller, O. Werz, G. Bifulco, J. Med. Chem. 54, 1565 (2011)

Article PubMed Google Scholar

15. B. Zhang, Eur. J. Med. Chem. 168, 357 (2019)

Article CAS PubMed Google Scholar

16. N. Fu, S. Wang, Y. Zhang, C. Zhang, D. Yang, L. Weng, B. Zhao, L. Wang, Eur. J. Med. Chem. 136, 596 (2017)

Article CAS PubMed Google Scholar

17. S.G. Agalave, S.R. Maujan, V.S. Pore, Chem. Asian J. 6, 2696 (2011)

Article CAS PubMed Google Scholar

18. S. Hakimian, A. Cheng-Hakimian, G.D. Anderson, J.W. Miller, Expert Opin. Pharmacother. 8, 1931 (2007)

Article CAS PubMed Google Scholar

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)

Article CAS PubMed Google Scholar

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)

Article CAS PubMed Google Scholar

21. C. Menendez, S. Gau, C. Lherbet, F. Rodriguez, C. Inard, M.R. Pasca, M. Baltas, Eur. J. Med. Chem. 46, 5524 (2011)

Article CAS PubMed Google Scholar

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)

Article CAS PubMed PubMed Central Google Scholar

24. M. Allam, A.K.D. Bhavani, A. Mudiraj, N. Ranjan, M. Thippana, P.P. Babu, Eur. J. Med. Chem. 156, 43 (2018)

Article CAS PubMed Google Scholar

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)

Article CAS PubMed Google Scholar

26. S. Rekha, U. Shantharam, V. Chandy, Int. Res. J. Pharm. 2, 81 (2011)

CAS Google Scholar

27. J. Sindhu, H. Singh, J.M. Khurana, C. Sharma, K.R. Aneja, Chin. Chem. Lett. 26, 50 (2015)

Article CAS Google Scholar

28. S. Ponnuchamy, S. Kanchithalaivan, R.R. Kumar, M.A. Ali, T.S. Choon, Bioorg. Med. Chem. Lett. 24, 1089 (2014)

Article CAS PubMed Google Scholar

29. D. Havrylyuk, B. Zimenkovsky, O. Vasylenko, C.W. Day, D.F. Smee, P. Grellier, R. Lesyk, Eur. J. Med. Chem. 66, 228 (2013)

Article CAS PubMed PubMed Central Google Scholar

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)

Article CAS PubMed Google Scholar

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)

Article CAS Google Scholar

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)

Article CAS PubMed Google Scholar

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)

Article CAS PubMed Google Scholar

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)

Article Google Scholar

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)

Article Google Scholar

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)

Article CAS PubMed PubMed Central Google Scholar

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)

Article CAS PubMed Google Scholar

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)

Article CAS PubMed Google Scholar

41. A. Maleki, A. Sarvary, RSC Adv. 5, 60938 (2015)

Article CAS Google Scholar

42. A. Maleki, V. Eskandarpour, Jour. of Iran. Chem. Soc. 16, 1459 (2019)

Article CAS Google Scholar

43. A.T. Kal-Koshvandi, M.R. Ahghari, A. Maleki, New J. Chem. 44, 12619 (2020)

Article Google Scholar

44. A. Maleki, M. Panahzadeh, R. Eivazzadeh-keihan, Green Chem. Lett and Rev. 12, 395 (2019)

Article CAS Google Scholar

45. A.A. Ali, M. Konwar, M. Chetia, D. Sarma, Tetrahedron Lett. 57, 5661 (2016)

Article CAS Google Scholar

46. M. Tavassoli, A.L. Isfahani, M. Moghadam, S. Tangestaninejad, V. Mirkhani, I.M. Baltork, ACS Sustainable Chem. Eng. 4, 1454 (2016)

Article CAS Google Scholar

47. M. Dabiri, S.K. Movahed, D.I. MaGee, Res. Chem. Intermed. 41, 3335 (2015)

Article CAS Google Scholar

48. H. Singh, J. Sindhu, J.M. Khurana, C. Sharma, K.R. Aneja, Eur. J. Med. Chem. 77, 145 (2014)

Article CAS PubMed Google Scholar

49. A.Z. Ahmady, F. Heidarizadeh, M. Keshavarz, Synth. Commun. 43, 2100 (2013)

Article CAS Google Scholar

50. A. Marra, A. Vecchi, C. Chiappe, B. Melai, A. Dondoni, J. Org. Chem. 73, 2458 (2008)

Article CAS PubMed Google Scholar

51. Y.B. Zhao, Z.Y. Yan, Y.M. Liang, Tetrahedron Lett. 47, 1545 (2006)

Article CAS Google Scholar

52. G. Wang, Z. Peng, J. Wang, X. Li, J. Li, Eur. J. Med. Chem. 125, 423 (2017)

Article CAS PubMed Google Scholar

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)

Article CAS PubMed Google Scholar

55. V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, Angew. Chem. Int. Ed. 41, 2596 (2002)

Article CAS Google Scholar

56. J. Sultana, N.D. Khupse, S. Chakrabarti, P. Chattopadhyay, D. Sarma, Tetrahedron Lett. 60, 1117 (2019)

Article CAS Google Scholar

57. Z. Zhang, Q. Zhou, F. Ye, Y. Xia, G. Wu, M.L. Hossain, Y. Zhang, J. Wang, Adv. Synth. Catal. 357, 2277 (2015)

Article CAS Google Scholar

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)

Article CAS Google Scholar

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)

Article CAS PubMed Google Scholar

62. K. Yamamoto, T. Bruun, J.Y. Kim, L. Zhang, M. Lautens, Org. Lett. 18, 2644 (2016)

Article CAS PubMed Google Scholar

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)

Article CAS PubMed Google Scholar

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Ethics declarations

Conflict of interest

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

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Cite this article

Kulkarni, P.S., Karale, S.N., Khandebharad, A.U. *et al.* Synthesis of novel 1,2,3-triazoles bearing 2,4 thiazolidinediones conjugates and their biological evaluation. *J IRAN CHEM SOC* 18, 2035–2046 (2021). https://doi.org/10.1007/s13738-021-02160-9

Received	Accepted	Published
12 June 2020	02 January 2021	19 January 2021

Issue Date

August 2021

DOI
https://doi.org/10.1007/s13738-021-02160-9

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Keywords

1,2,3-Triazoles 2,4 Thiazolidinedione Amide and Ethereal linkage

Anti-mycobacterial activity Cytotoxicity study