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Synthesis and Antimicrobial Activity of (*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides

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ABSTRACT

In current times, researchers adopted the click chemistry approach for the synthesis of various drug-like molecules by using a few reliable, feasible, practical and selective chemical transformations *via* click formation. In present work, we focussed on the most triazole clubbed thiazolidine-2,4-dione derivatives as the most promising motifs for broad biological application. A total of fifteen (**CF-4a-o**) derivatives were synthesized and well characterized with various analytical techniques.

KEYWORDS

1,2,3-Triazole, Thiazolidine-2,4-dione, Triazole clubbed thiazolidine-2,4-dione, Click chemistry, Antimicrobial activity, Antifungal activity.

INTRODUCTION

In the last two decades, high-throughput screening and combinatorial chemistry has advanced. Thus, synthetic chemistry, the traditional science of structural modifications and synthesis of compounds, has undertaken the challenging task of medicine oriented synthesis [1]. Achieving favourable biological functions through the diversity of molecular assemblies and generation of molecules remains a challenge. In the conventional synthetic approaches, immediate refinement is essential. Novel and highly efficient methodologies and chemical reactions, which can reduce purification steps and difficult protection–deprotection in conventional fabrication processes, must be developed for chemical research revolution [2]. Different synthetic methodologies have gained attention of researchers for the construction of new molecules with potential uses in the field of biology and most-promising functional groups in a biological system [3]. Synthesis methods using a modular approach to effectively produce biologically significant motifs are highly crucial for molecular probe production, pharmaceutical development and screening assays.

Sharpless [4] coined the term 'click chemistry' for defining a group of reactions with a high yield, stereospecific, wide range of scope and limited or zero byproducts. In addition to considerable success, click-chemistry based drug discovery

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methods provide simplified syntheses, offering a fast approach to optimization and discovery. Click reactions present properties such as stereospecificity (but not necessarily enantioselectivity), wide scope, simple reaction conditions, high yields and low amounts of impurities, which can be eliminated using the non-chromatographic method as well as are modular [5]. For these reactions, reagents and starting materials readily available, a solvent is not required or an easily removable or a benign solvent (such as water) can be used and product isolation is simple. Moreover, impurities can be easily removed. If required, purification must be performed using a non-chromatographic method, including distillation or crystallization. Furthermore, under physiological conditions, the product is stable [6,7]. The click chemistry approach involves the condensation of alkyne groups with organic azides to produce 1,2,3-triazole linkage [8]. Alkyne and azide groups are easily incorporated into a scaffold of a large organic structure of biological-active molecules.

Triazoles nuclei are well-known and the most important heterocycles, which are an integral and common part of various medicinal agents and natural products [9]. Triazoles and their homologs have received considerable attention because of their chemotherapeutic importance [10,11]. Studies have suggested that triazole derivatives present numerous pharmacological activities, including antimicrobial [12,13], analgesic [14], local anaesthetic, anti-inflammatory [15], anticonvulsant [16], antineoplastic [17,18], antiviral [19], antiproliferative [20] and anticancer [21] activities. Thiazolidinone scaffolds have become highly potent scaffolds and have gained keen research attention because of their diverse biological applications. A thiazolidinediones is a saturated thiazole, also known as thiazolidine, having one carbonyl group. Because of their flexible and diverse nature, thiazolidinediones exhibit numerous pharmacological activities, such as antihyperglycemic [22], antimicrobial [23], antiviral [24], antioxidant [25], aldose reductase inhibition [26], α-glucosidase inhibition [27], anticancer [28], anti-plasmodial [29], β-3 agonists [30], hypolipidemic activities [31], neuroprotective [32] and tyrosinase inhibition [33]. 1,3-Thiazolidin-4-one presents various pharmacological activities, including antidiabetic, anticancer, antimicrobial, anti-inflammatory, antiviral and anticonvulsant activities [34]. This article summarizes different synthesis approaches to the synthesis of triazole-clubbed thiazolidine-2,4-dione derivatives and their biological significance.

EXPERIMENTAL

All the chemicals are used to carry out this work were of the Analytical grade (A.R.) or laboratory-grade (L.R) and were procured from Spectrochem Mumbai, Loba Chemie, Rankem, Sigma-Aldrich and S.D. Fine Chemicals. TLC (thin layer chromatography) was observed on 0.2 mm pre-coated plates of silica gel G60 F_{254} (Merck). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in the open capillaries method, which are uncorrected.

Fourier transforms infrared (FTIR) spectra were recorded in the spectral range 4000-400 cm^{-1} on Shimadzu FT-IR model no 8400 infinity. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in ESI (70 eV) model using direct inlet probe technique and *m/z* is reported in atomic units per elementary charge. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-III 400 MHz spectrometer 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR DMSO-d_6 were used as the solvents.

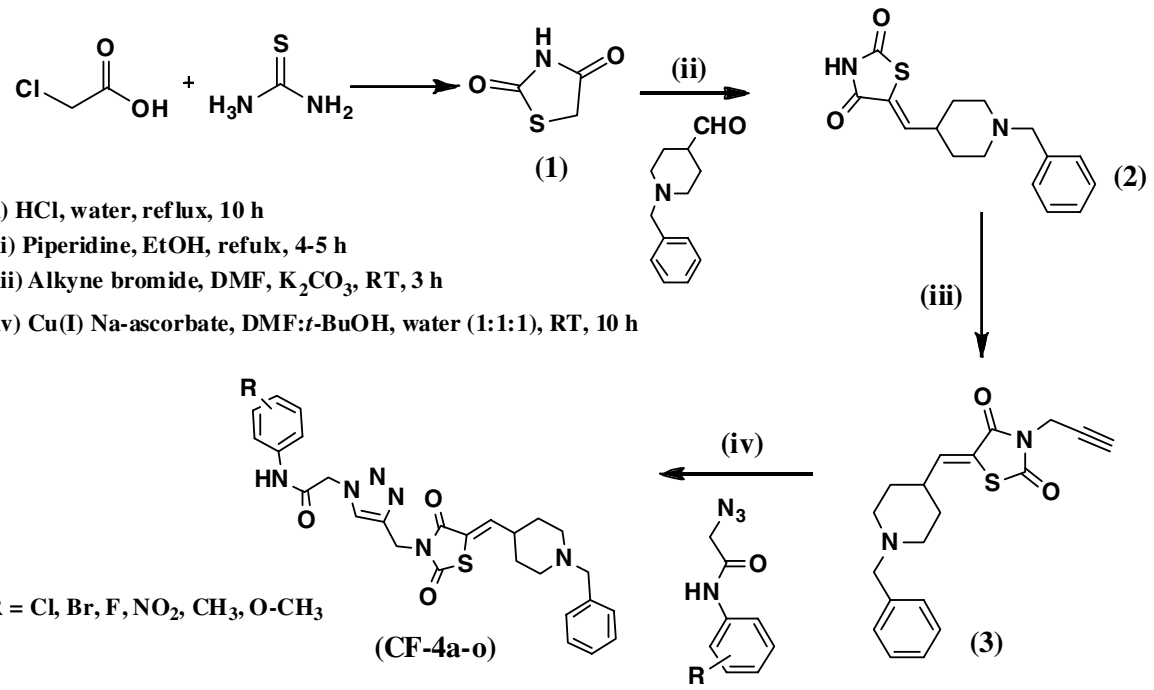
General procedure for the synthesis of thiozolidine-2,4-dione (1): Round bottom flask charged with 2-chloroacetic acid (1 mmol) and thiourea (1 mmol) was dissolved in distilled water allowed to be stirred for 30 min, the white precipitates were obtained, add few drops of conc. HCl after precipitates and further reflux for 10 h. Monitoring of reaction was checked by TLC and after completion of reaction, product collected and dried over vacuum and recrystallized from water; white solid, yield 78%; m.p.: 118-120 ºC.

General procedure for the synthesis of 5-((1-benzylpiperidin-4-yl)methylene)thiazolidine-2,4-dione (2): The compound **2** was synthesized from a mixture of thiazolidine-2,4-dione (**1**) (1 mmol), aldehyde (1 mmol), in ethanol as solvent and add few drops of piperidine as a catalyst. The reaction mixture was heated under reflux and continuously stirred for a period of 4-5 h. The progress of the reaction was monitored by TLC. The reaction mixture was poured into ice-cold water. The resulting precipitate was filtered off and recrystallized from methanol (**2**) off-white, yield 80%, m.p.: 130-132 ºC.

General procedure for the synthesis of 5-((1-benzylpiperidin-4-yl)methylene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (3): Formation of the product **3** was carried out by utilizing compound **2** (1 mmol) and appropriate alkyne bromide (1.2 mmol) dissolved in DMF, add anhydrous K_2CO_3 (2 mmol) in the reaction mixture. The reaction mixture was allowed to stir for 3 h at room temperature. The progress of the reaction was monitored using thin-layer chromatography, after the completion of the reaction, the reaction mass was poured into crushed ice, the grey-coloured semi-solid product was obtained. The obtaining reaction collected and filtered off and recrystallized from ethyl acetate (**3**) cream-coloured, yield 65%, m.p.: 110-112 ºC.

General procedure for the synthesis of 2-azido-*N*-phenylacetamide derivatives: Substituted 2-azido-*N*-phenylacetamide derivatives were synthesized by chloroacetylation of substituted aromatic amines with chloroacetyl chloride in an aqueous medium in presence of K_2CO_3. Then, the obtained substituted 2-chloro-*N*-phenylacetamide were reacted with sodium azide in DMF at room temperature to furnish the corresponding reaction and obtaining the product utilized for the next step (**CF-4a-o**) (**Scheme-I**).

General procedure for the synthesis of 2-(4-((5-((1-benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (CF-4a-o): Synthesis of novel 1,2,3- triazole derivatives (**CF-4a-o**) obtained with the mixture of 5-((1-benzylpiperidin-4-yl)-methylene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**3**) (1 mmol), 2-azido-*N*-phenylacetamide (1 mmol), copper sulphate (0.08 mmol) and sodium ascorbate (0.16 mmol) in DMF: *t*-BuOH:water (1:1:1:) ratio and stirred at room temperature for 10 h. After completion of the reaction (monitored by TLC), the resultant reaction mixture ware poured into crushed ice and obtain precipitate was filtered off, washed with cold water, reaction mass quenched in ammonium chloride solution to



Scheme-I: General reaction scheme

remove excess copper and purified by crystallization with hot methanol to afford desire product (**CF-4a-o**).

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-methoxy-4-nitrophenyl)acetamide (CF-4a): Grey solid, yield: 77%, m.f.: $C_{28}H_{29}N_7O_6S$, R_f value: 0.42, m.p.: 122-124 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3333, 3155, 2939, 2800, 1743, 1689, 1635, 1504, 1342, 1234, 1149, 1095, 1033, 964, 856, 794, 740, 655, 555, 462, MS: (*m/z*): 592. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.23 (s, 1H), 8.34 (d, *J* = 5.2 Hz, 1H), 8.13 (s, 1H), 7.88 (s, 2H), 7.38 (s, 5H), 7.0 (s, 1H), 5.52 (s, 2H), 4.89 (s,2H), 3.84 (s, 3H), 3.54 (s, 2H), 2.85 (s, 2H), 2.16 (s, 3H), 1.67 (s, 2H), 1.59 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.05, 169.15, 167.71, 150.44, 142.71, 142.38, 137.79, 136.79, 131.20, 128.57, 128.55, 127.65, 125.41, 122.90, 120.94, 117.07, 106.20, 63.16, 56.70, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-fluorophenyl)acetamide (CF-4b): Off white solid, yield: 82%, m.f.: $C_{27}H_{27}N_6O_3SF$, R_f value: 0.40, m.p.: 132-134 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3147, 3047, 2947, 2762, 1882, 1743, 1689, 1627, 1566, 1512, 1388, 1334, 1219, 1149, 1057, 964, 833, 740, 694, 609, 563, 509,MS (*m/z*): 535. ^{1}H NMR (400 MHz, DMSO) δ 10.58 (s, 1H), 8.12 (s, 1H), 7.60 (s, 2H), 7.34 (s, 4H), 7.18 (t, *J* = 8.3 Hz, 3H), 6.99 (d, *J* = 8.5 Hz, 1H), 5.30 (s, 2H), 4.87 (s, 2H), 3.55 (s, 2H), 2.88 (s, 2H), 2.17 (s, 3H), 1.68 (s, 2H), 1.60 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.05, 169.15, 168.25, 159.17, 156.65, 142.38, 137.79, 136.79, 135.87, 135.84, 128.57, 128.55, 127.65, 125.41, 122.90, 121.90, 121.82, 115.58, 115.38, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-chloro-2-nitrophenyl)acetamide (CF-4c): Dark grey solid, yield: 78%, m.f.: $C_{27}H_{26}N_7O_5SCl$, R_f value: 0.55, m.p.: 162-164 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3309, 3155, 2939, 2769, 2114, 1944, 1681, 1504, 1442, 1334, 1273, 1149, 1057, 972, 840, 740, 663, 516, MS: (*m/z*): 596. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.85 (s, 1H), 8.10 (s, 2H), 7.83 (s, 1H), 7.74 (s, 1H), 7.33 (s, 5H), 7.02 (d, *J* = 7.2 Hz, 1H), 5.42 (s, 2H), 4.88 (s, 2H), 3.54 (s, 2H), 2.86 (s, 2H), 2.16 (s, 3H), 1.68 (s, 2H), 1.60 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.05, 169.15, 167.71, 142.38, 137.79, 136.95, 136.79, 136.75, 130.78, 128.57, 128.55, 127.65, 126.93, 126.25, 125.41, 123.68, 122.90, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-nitrophenyl)acetamide (CF-4d): Grey solid, yield: 95%, m.f.: $C_{27}H_{27}N_7O_5S$, R_f value: 0.37, m.p.: 158-160 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3217, 3147, 2939, 2808, 2360, 2114, 1689, 1558, 1512, 1342, 1265, 1111, 972, 856, 748,702, 493,MS: (*m/z*): 562. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.22 (s, 1H), 8.27 (d, *J* = 9.2 Hz, 2H), 8.14 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.33-7.27 (m, 5H), 6.99 (d, *J* = 9.2 Hz, 1H), 5.41 (s, 2H), 4.88 (s, 2H), 3.54 (s, 2H), 2.85 (s, 2H), 2.16 (s, 3H), 1.67 (s, 2H), 1.59 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.68, 165.27, 164.02, 144.46, 142.55, 141.85, 140.77, 129.00, 128.10, 127.05, 125.31, 125.06, 123.34, 119.01, 52.19, 51.73, 36.36, 29.38.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(3,4-dichlorophenyl)acetamide (CF-4e): Dark grey solid, yield: 84%, m.f.: $C_{27}H_{26}N_6O_3SCl_2$, R_f value: 0.41, m.p.: 160-162 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3155, 3093, 3039, 2939, 2800, 1681, 1597, 1527, 1465, 1381, 1234, 1141, 1057, 972, 864, 817, 740, 663,555, MS (*m/z*): 585. ^{1}H NMR (400 MHz, DMSO): δ 10.80 (s, 1H), 8.12 (s, 1H), 7.95 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.34 (s, 5H), 7.00 (d, *J* = 8.8 Hz, 1H), 5.34 (s, 2H), 4.87 (s, 2H), 3.59 (s, 2H), 2.90 (s, 2H), 2.18 (s, 3H), 1.68 (s, 2H), 1.60 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.05, 169.15, 168.25, 142.38, 137.79,

136.79, 134.21, 131.84, 128.81, 128.57, 128.55, 127.65, 125.41, 124.78, 123.75, 122.90, 119.36, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(3-chloro-4-fluorophenyl)acetamide (CF-4f): Off white solid, yield: 88%, m.f.: $C_{27}H_{26}N_6O_3SClF$, R_f value: 0.35, m.p.: 138-140 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3333, 3147, 3055, 2939, 2800, 1890, 1681, 1543, 1496, 1381, 1327, 1219, 1141, 1057, 964, 817, 740, 563, 509, MS (*m/z*): 562(M^{+2}). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.71 (s, 1H), 8.14 (s, 1H), 7.89 (s, 1H), 7.44 (d, *J* = 9.2 Hz, 2H), 7.33 (s, 5H), 7.02 (d, *J* = 8.8 Hz, 1H), 5.34 (s, 2H), 4.89 (s, 2H), 3.49 (s, 2H), 2.82 (s, 2H), 2.14 (s, 3H), 1.66 (s, 2H), 1.58 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.69, 164.48, 164.06, 152.16, 142.02, 135.48, 128.75, 128.05, 126.81, 125.20, 123.21, 120.70, 119.62, 119.36, 119.17, 117.25, 117.01, 62.27, 52.00, 36.36, 29.70.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-chlorophenyl)acetamide (CF-4g): Light grey solid, yield: 92%, m.f.: $C_{27}H_{27}N_6O_3SCl$, R_f value: 0.45, m.p.: 146-148 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3186, 3039, 2939, 2800, 1890, 1689, 1627, 1543, 1489, 1381, 1334, 1242,1149,1095, 964,833, 732, 563, 509, MS (*m/z*): 551 (M^{+2}). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.70 (s, 1H), 8.13 (s, 1H), 7.63 (s, 2H), 7.37 (s, 4H), 7.19 (t, *J* = 8.3 Hz, 3H), 7.01 (d, *J* = 8.5 Hz, 1H), 5.33 (s, 2H), 4.89 (s, 2H), 3.59 (s, 2H), 2.88 (s, 2H), 2.18 (s, 3H), 1.69 (s, 2H), 1.62 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.05, 169.15, 168.25, 142.38, 137.79, 136.79, 136.76, 129.15, 128.57, 128.55, 127.84, 127.65, 125.41, 122.90, 121.59, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(3,4-dimethylphenyl)acetamide (CF-4h): Grey solid, yield: 75%, m.f.: $C_{29}H_{32}N_6O_3S$, R_f value: 0.50, m.p.: 152-154 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3294, 3147, 3047, 2939, 2793, 1890, 1681, 1543, 1388, 1319, 1234, 1149, 1049, 964, 810, 748, 555, 493, MS: (*m/z*): 545. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (s, 1H), 7.78-7.74 (m, 2H), 7.56-7.49 (m, 1H), 7.26 (s, 6H), 7.00 (d, *J* = 8.8 Hz, 1H), 5.34 (s, 2H), 4.87 (s, 2H), 3.59 (s, 2H), 2.90 (s, 2H), 2.34 (s, 3H), 2.21 (s, 3H), 2.18 (d, *J* = 1.1 Hz, 3H), 1.64 (s, 2H), 1.58 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.05, 169.15, 168.25, 142.38, 137.79, 137.74, 137.03, 136.79, 134.44, 129.64, 128.57, 128.55, 127.65, 125.41, 122.90, 122.81, 117.33, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-fluorophenyl)acetamide (CF-4i): Light grey solid, yield: 80%, m.f.: $C_{27}H_{27}N_6O_3SF$, R_f value: 0.40, m.p.: 128-130 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3140, 3055, 2947, 2831, 1905, 1743, 1689, 1627, 1550, 1450, 1373, 1203, 1141, 964, 925, 864, 748, 702, 555, 455, MS: (*m/z*): 535. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.31 (s, 1H), 8.12 (s, 1H), 7.90 (s, 1H), 7.34 (s, 6H), 7.19 (s, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 5.40 (s, 2H), 4.87 (s, 2H), 3.57 (s, 2H), 2.88 (s, 2H), 2.18 (s, 3H), 1.68 (s, 2H), 1.60 (s, 2H). ^{13}C NMR (10 MHz, DMSO-d_6): δ 166.68, 164.73, 164.07, 154.59, 152.16, 141.72, 140.72, 129.05, 128.12, 127.10, 125.64, 125.37, 125.22, 124.40, 123.68, 123.30, 115.60, 115.41, 61.74, 51.85, 51.70, 36.37, 29.32.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-bromophenyl)acetamide (CF-4j): Off white solid, yield: 78%, m.f.: $C_{27}H_{27}N_6O_3SBr$, R_f value: 0.47, m.p.: 158-160 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3147, 3039, 2947, 2800, 1898, 1689, 1627, 1543, 1489, 1388, 1334, 1242, 1149, 1064, 964, 825, 732, 655, 563, 501, MS (*m/z*): 595 (M^{+2}). ^{1}H NMR (400 MHz, DMSO): δ 10.74 (s, 1H), 8.11 (s, 1H), 7.66 (s, 2H), 7.41 (s, 4H), 7.20 (t, *J* = 8.3 Hz, 3H), 7.03 (d, *J* = 8.5 Hz, 1H), 5.32 (s, 2H), 4.88 (s, 2H), 3.61 (s, 2H), 2.86 (s, 2H), 2.19 (s, 3H), 1.67 (s, 2H), 1.61 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.05, 169.15, 168.25, 142.38, 137.79, 136.79, 136.60, 131.88, 128.57, 128.55, 127.65, 125.41, 122.90, 121.62, 119.56, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2,5-dichlorophenyl)acetamide (CF-4k): Grey solid, yield: 74%, m.f.: $C_{27}H_{26}N_6O_3SCl_2$, R_f value: 0.41, m.p.: 144-146 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3271, 2931, 2800, 2368, 1689, 1589, 1527, 1373, 1334, 1273, 1149, 1095, 1049, 972, 918, 802,740, 694, 648, 594, 547, 439, MS (*m/z*): 585. ^{1}H NMR (400 MHz, DMSO): δ 10.19 (s, 1H), 8.12 (s, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.29 (m, 6H), 6.98 (d, *J* = 9.6 Hz, 1H), 5.44 (s, 2H), 4.87 (s, 2H), 3.50 (s, 2H), 2.84 (s, 2H), 2.17 (s, 3H), 1.66 (s, 2H), 1.55 (s, 2H), ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.05, 169.15, 167.71, 142.38, 137.79, 136.93, 136.79, 133.11, 129.81, 128.57, 128.55, 127.65, 126.48, 125.41, 122.90, 122.64, 121.97, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(*p*-tolyl)acetamide (CF-4l): Grey solid, yield: 85%, m.f.: $C_{28}H_{30}N_6O_3S$, R_f value: 0.48, m.p.: 142-144 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3132, 3032, 2939, 2847, 1743, 1689, 1543, 1327, 1249, 1141, 964, 817, 748, 702, 509, MS (*m/z*): 531. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (s, 1H), 7.87 (s, 2H), 7.64 (s, 2H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.31-7.29 (m, 5H), 7.03 (d, *J* = 9.3 Hz, 1H), 5.41 (s, 2H), 4.88 (s, 2H), 3.54 (s, 2H), 2.85 (s, 2H), 2.24 (s, 3H), 2.16 (s, 3H), 1.67 (s, 2H), 1.59 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.05, 169.15, 168.25, 142.38, 137.79, 136.79, 132.06, 129.69, 128.57, 128.55, 127.65, 125.41, 122.90, 119.96, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-nitrophenyl)acetamide (CF-4m): Dark grey solid, yield: 72%, m.f.: $C_{27}H_{27}N_7O_5S$, R_f value: 0.37, m.p.: 130-132 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3325, 3140, 2939, 2800, 2762, 1959, 1882, 1689, 1597, 1504, 1435, 1334, 1280, 1141, 1057, 964, 840, 740, 655, 509, MS (*m/z*): 562. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.73 (s, 1H), 8.14 (s, 1H), 7.93 (s, 1H), 7.37 (s, 6H), 7.17 (s, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 5.44 (s, 2H), 4.86 (s, 2H), 3.59 (s, 2H), 2.91 (s, 2H), 2.16 (s, 3H), 1.67 (s, 2H), 1.58 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.05, 169.15, 167.71, 142.38, 137.79, 137.38, 136.79, 136.01, 134.04, 128.57, 128.55, 127.65, 126.28, 125.41, 122.90, 121.29, 120.78, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2,4-dimethylphenyl)acetamide (CF-4n): Grey solid, yield: 82%, m.f.: $C_{29}H_{32}N_6O_3S$, R_f value: 0.50, m.p.: 118-120 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3302, 3147, 3047, 2931, 2800, 1681, 1543, 1381, 1327, 1226, 1149, 1057, 972, 817, 748, 555, 501, 447, MS (*m/z*): 544. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.93 (s, 1H), 7.77-7.72 (m, 2H), 7.53-7.47 (m, 1H), 7.25 (s, 6H), 7.06 (d, *J* = 8.7 Hz, 1H), 5.33 (s, 2H), 4.85 (s, 2H), 3.57 (s, 2H), 2.93 (s, 2H), 2.33 (s, 3H), 2.24 (s, 3H), 2.17 (s, 3H), 1.64 (s, 2H), 1.58 (s, 2H). ^{13}C NMR (100 MHz DMSO-d_6): δ 180.05, 169.15, 167.71, 142.38, 137.79, 136.79, 136.23, 130.50, 128.57, 128.55, 127.65, 126.83, 126.56, 126.02, 125.41, 122.90, 120.63, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

(*Z*)-2-(4-((5-((1-Benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(3-chlorophenyl)acetamide (CF-4o): Light grey solid, yield: 82%, m.f.: $C_{27}H_{27}N_6O_3SCl$, R_f value: 0.45, m.p.: 156-158 ºC, FT-IR (KBr, ν_{max}, cm^{-1}): 3188, 3040, 2936, 2800, 1890, 1690, 1628, 1544, 1490, 1380, 1335, 1244, 1150, 1096, 964, 834, 736, 564, 508, MS (*m/z*): 551 (M^{+2}). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.53 (s, 1H), 7.92 (s, 1H), 7.62 (s, 1H), 7.57 (s, 2H), 7.42 (s, 1H), 7.25 (s, 5H), 7.04 (d, *J* = 8.3 Hz, 1H), 5.31 (s, 2H), 4.93 (s, 2H), 3.60 (s, 2H), 2.86 (s, 2H), 2.17 (s, 3H), 1.71 (s, 2H), 1.59 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 180.05, 169.15, 168.25, 142.38, 139.28, 137.79, 136.79, 133.67, 129.68, 128.57, 128.55, 127.65, 125.41, 123.58, 122.90, 120.91, 120.19, 63.16, 51.02, 50.91, 45.57, 35.60, 28.04.

Biological evaluation: The synthesized analogous of thiazolidine-2,4-dione clubbed 1,2,3-triazole derivatives (**CF-4a-j**) were screened for *in vitro* antibacterial potential against two Gram-negative and Gram-positive bacterial strain and fungal strain respectively *i.e. Staphylococcus aureus* & *Bacillus megaterium, Enterobacter aerogenes* & *Salmonella typhi* and *Aspergillus flavus* & *Aspergillus niger* using Muller-Hinton broth dilution method using stock solutions of 1000 and 500 µg/mL.

Method: Liquid cultures of bacteria at suitable growth phase, sterile Petri dishes, sterile 96-well microtiter plates (round-bottom wells are best), filter-sterilized antibiotics, sterile diluents, test tubes and dimethyl sulphoxide (DMSO) was applied as solvent control. The pure test microbial strains grew in the Muller-Hinton broth for 24 h. Bacterial strains were incubated at 37 ºC, whereas 28 ºC was provided for fungi.

The stock solution of standard antibiotics ampicillin, streptomycin and nystatin were prepared in DMSO solvent. Dispense 2 mL of Muller-Hinton broth into the first tube and 1 mL broth in all other tubes. Pour the drug into the first tube to make up the final concentration as 1000 µg/mL. Mixed the drug with media thoroughly. Withdrew 1 mL antibiotic solution and transferred into next tube. The concentration of the second tube will be reached to 500 µg/mL. Mixed up and dilute 6-8 times and again transferred 1 mL of antibiotic solution to the third tube containing broth. Similarly, serial dilution can be performed up to 62.5 µg/mL. Discard 1mL antibiotic solution from the last tube. Mid-log cultured microbes were diluted and adjust the bacterial growth to get a cell turbidity equivalence to the McFarland 0.5 standard. This dilution will be equivalent to bacterial cell density 4×10^5 to 5×10^5 cfu/mL. Fungal growth will be equivalent to $1\text{-}5 \times 10^5$ cfu/mL. 5 µL of all the microbes from tube 1 to tube 5. Incubated the tubes for 24-48 h at the desired temperature of bacteria and fungi. The positive control only has the drug solution added to the broth and the negative control only has the microorganisms inoculated in the broth. When satisfactory growth is obtained, the absorbance of microbes were taken at 600 nm.

RESULTS AND DISCUSSION

Various 1,4-disubstituted 1,2,3-triazoles *i.e.* 2-(4-((4-substituted phenoxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-aryl-acetamides (**CF-4a-o**) were synthesized *via* copper(I)-catalyzed click reaction of (*Z*)-5-((1-benzylpiperidin-4-yl)methylene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione with 2-azido-*N*-aryl-acetamides. 2-Azido-*N*-arylacetamides were synthesized by reacting corresponding 2-choloro-*N*-arylacetamides with aqueous sodium azide. (*Z*)-5-((1-Benzylpiperidin-4-yl)-methylene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione were synthesized by reacting propargyl bromide with (*Z*)-5-((1-benzylpiperidin-4-yl)methylene)thiazolidine-2,4-dione using K_2CO_3 as a base in dimethylformamide, whereas 2-choloro-*N*-arylacetamides were synthesized by reacting chloro acetyl chloride with various aromatic amines using K_2CO_3 as base in acetone. The terminal alkynes *i.e.* (*Z*)-5-((1-benzylpiperidin-4-yl)methylene)-3-(prop-2-yn-1-yl) thiaz olidine-2,4-dione were reacted with 2-choloro-*N*-arylacetamides in the presence of sodium azide, copper sulphate pentahydrate and sodium ascorbate in dimethylformamide-water-*t*-BuOH, to furnish desired (*Z*)-2-(4-((5-((1-benzylpiperidin-4-yl)methylene)-2,4-dioxothiazolidin-3-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenyl-acetamides (**CF-4a-o**). Synthesized 1,4-disubstituted 1,2,3-triazoles (**CF-4a-o**) were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

Some limited optimizations were performed to establish effective and mild reaction conditions for the synthesis of compounds (**CF-4a-o**). Initially, a reaction in the presence of Cu(I) catalyzed in various solvents or a mixture of solvents, based on the previously reported conventional method is shown in Table-1, entry 1-8. To quicker reaction time as well as easiest and mild reaction conditions, the reaction performs as per entry in Table-1, entry 6-10. Based on all the above trial reactions, the model reaction conditions for the synthesis of the targete compounds using ultrasonic irradiation and DMF:*t*-BuOH: water (1:1:1) as a solvent (Table-1, entry 4 and 6) to achieve good yields, shorter reaction times and further no requirement for crystallization and any purification.

Biological activity: The potency against various microbial strains as a Gram-positive and Gram-negative bacteria and also antifungal strain using Muller-Hinton broth dilution method was evaluated against the synthesized triazole clubbed thiazolidine-2,4-dione derivatives. Among the synthesized compounds, compounds **CF-4c, CF-4i** and **CF-4j** were found to be most effective against Gram-positive bacteria, Gram-negative bacteria as well as fungi (Table-2). Compounds **CF-4a, CF-4c, CF-4d, CF-4e, CF-4f, CF-4i** and **CF-4j** were very effective broad-spectrum drug, which can inhibit the growth of both Gram-positive and Gram-negative bacteria. Compounds

TABLE-1
OPTIMIZATION CONDITIONS FOR COMPOUND **CF-4d**

Entry	Solvent	Catalyst	Reducing agent	Yield (%)
1	MeOH	$CuSO_4 \cdot 5H_2O$	Sodium ascorbate	58
2	DMF + *t*-BuOH + water (2:1:2)	$CuSO_4 \cdot 5H_2O$	–	Traces
3	DMF + *t*-BuOH + water (2:1:2)	$CuSO_4 \cdot 5H_2O$	Sodium ascorbate	80
4	DMF + *t*-BuOH + water (2:1:2)	$Cu(OAc)_2$	Sodium ascorbate	84
5	DMF + *t*-BuOH + water (2:1:2)	$Cu(OAc)_2$	–	Traces
6	DMF + *t*-BuOH + water (1:1:1)	$CuSO_4 \cdot 5H_2O$	Sodium ascorbate	95
7	*t*-BuOH	$CuSO_4 \cdot 5H_2O$	Sodium ascorbate	42
8	DMF	$CuSO_4 \cdot 5H_2O$	Sodium ascorbate	78

Reaction condition: Starting materials 5-((1-benzylpiperidin-4-yl)methylene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**3**) (1 mmol), azido-*N*-phenylacetamide (1 mmol), 0.2 equiv. of appropriate Cu-sources, reducing agent and solvent.

TABLE-2
ANTIMICROBIAL ACTIVITY OF THIAZOLIDINE CLUBBED 1,2,3-TRIAZOL DERIVATIVES (**CF-4a-j**)

Compounds	*Staphylococcus aureus*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Aspergillus paraciticus*	*Rhizopus*
Streptomycin	–	–	50	50	–	–
Ampicillin	100	100	–	–	–	–
Nystatin	–	–	–	–	100	100
CF-4a	125	125	125	125	1000	1000
CF-4b	500	500	1000	1000	1000	1000
CF-4c	250	250	500	500	125	500
CF-4d	62.5	62.5	62.5	62.5	62.5	1000
CF-4e	250	250	250	500	1000	1000
CF-4f	62.5	62.5	500	125	1000	1000
CF-4g	1000	1000	1000	1000	1000	1000
CF-4h	1000	1000	1000	1000	62.5	1000
CF-4i	250	250	250	250	250	500
CF-4j	250	250	1000	125	62.5	62.5

CF-4c exhibited antibacterial activity against Gram-positive bacteria; therefore, their mode of action should be probably the cell wall of bacteria, whereas compound **CF-4h** shows significant antifungal activity.

Conclusion

In this work, the successful development of a synthetic protocol for synthesis of triazole derivatives by using copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) click chemistry approach to synthesize various analogous of thiozolidine-2,4-dione clubbed 1,2,3-triazole containing core skeletons (**CF-4a-o**), characterized by mass, ^1H & ^{13}C NMR techniques and evaluated their potency against various microbial strains as a Gram-positive and Gram-negative bacteria and also antifungal strain using Muller-Hinton broth dilution method. The synthesized compounds **CF-4c, CF-4i** and **CF-4j** were found to be most effective against Gram-positive bacteria, Gram-negative bacteria as well as fungi. The significant results would be useful to develop a new strategy for the next target with better quality effectiveness and influence of molecules for an additional therapeutic position.

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