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ARTICLE

Efficient Synthesis of 5-(4-(Substituted [1,1′-Biphenyl]-4-yl-methoxy)benzyl)thiazolidine-2,4-diones under Microwave Irradiation using Suzuki Coupling Reaction and their Biological Screening

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ABSTRACT

In present study, an efficient and greener protocol is developed for the synthesis of 5-(4-(substituted [1,1′-biphenyl]-4-yl-methoxy)benzyl)-thiazolidine-2,4-diones by using microwave irradiations. Here, a one-pot reaction between 5-(4-((4-bromobenzyl)oxy)benzyl)thiazolidine-2,4-dione, substituted aryl boronic acid and K_2CO_3 in the presence of toluene:water:ethanol solvents under conventional heating methods and microwave irradiation methods is reported. All the final compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic analysis. The antimicrobial evaluation studies show moderate activities against used microbes.

KEYWORDS

Suzuki coupling reaction, Microwave synthesis, Antimicrobial activity, Thiazolidine-2,4-diones derivatives.

INTRODUCTION

Heterocyclic functioning organic compounds in which oxygen, nitrogen and sulphur atoms containing compounds are broadly assigned in nature and important in the field of biologically active molecules [1]. Among the thiazolidine-2,4-dione (TZD) [2] is the most important heterocyclic moiety with much attention particularly in the treatment of type 2 diabetes [3]. Thiazolidine-2,4-dione derivatives possess a significance role in broad range of pharmacological activity [4]. Therefore, the recent growth of research and enhance the interest for chemist who have prepared a variety of thiazolidinedione's derivatives and evaluated them for their various biological activities. Presently multiple antimicrobial [5] drugs are available in the market, but there is a requirements of the discovery of new lead structures and novel chemical entities which will act as antibacterial agents with better pharmacodynamics [6] and pharmacokinetic [7] properties with minimum side effects.

They shows a number of pharmacological activities such as antimicrobial [8], antitubercular, antioxidant [9], anti-tumor, anticancer [10], antiviral [11], anti-HIV, hyperglycemic [12], anti-inflammatory [13] and antidiabetic [9].

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Microwave-irradiation (MW) [14] technique is used to promote the organic chemical reactions and a multiple number of reviews have advocated in organic one-pot synthesis. Organic molecules synthesis using microwave irradiation method has merits over conventional heating method. Microwaves-assisted method provide a powerful way to carry out synthetic chemistry and they gave ability of shorten reaction times, increase reaction yields [15] and facilitate to reactions. Overall, microwave-assisted method allows conducting economical and cleaner reactions.

Efficient C-C bond formation [16] reactions have been in the limelight of catalysis research for the past few decades. Suzuki coupling [17] is one such reaction, in which coupling between an organo-boron reagent and an organic halide or pseudo halide takes place in presence of palladium catalyst, phosphine ligand and a base. Suzuki coupling is one of the most efficient methods for the synthesis of diaryl acetylenes that constitutes important building blocks. Miyaura cross-coupling [18] reaction is one such prominent reaction plays a key role in organic chemistry as well as evolved an important chemistry tool for in numerable appli-cations such as agrochemicals, polymers, synthetic intermediates, *etc.* are using microwaves and ultrasonic [19].

Pharmacological importance of thiazolidine-2,4-dione derivatives inspired us to synthesize new compounds (**V-XVI**) under conventional heating and microwave irradiation methods. Herein, a new, rapid and efficient synthetic method for 5-(4-(substituted [1,1′-biphenyl]-4-yl-methoxy)benzyl)thiazolidine-2,4-diones from 5-(4-((4-bromobenzyl)oxy)benzyl)thiazolidine-2,4-dione presence of K_2CO_3 base and $Pd(PPh_3)_4$ catalyst.

EXPERIMENTAL

All chemicals were purchased and used without any further purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel-G plates (G60 F_{254} (Merck)) of 0.5 mm thickness, visualizing was made with ultraviolet light (254 and 365 nm), or with iodine vapour chamber and aq. $KMnO_4$ reagent. Melting point was determined using a Buchi B-540 open capillary apparatus. IR spectra were recorded on a FTIR-8400 S, CE Shimadzu instrument using KBr pellets method and are expressed in cm^{-1}. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz and Bruker DRX 101 MHz spectrometer, respectively in deuterated solvents like $CDCl_3$ or DMSO-d_6 solvent. For Suzuki coupling the Monowe 300 (Anton Paar) microwave synthesizer was used. Solvents were evaporated with a Buchi rotary evaporator. The purification of all synthesized compounds was performed by borosil glass column having a length about 1000 mm.

Biological assay

Antibacterial assay: The broth dilution method was applied for the evaluation of the antibacterial activity. It is one of the non-automated *in vitro* bacterial susceptibility tests. This technique shows the quantitative result for the amount of antimicrobial agents needed to inhibit specific microorganisms' growth. The screened for their antibacterial activity in triplicate sets against these bacteria at different concentrations of 1000, 500, 250 and 200 µg/mL. The drugs which were found to be active in primary analysis were further diluted and evaluated. 10 µg/mL suspension was also inoculated on appropriate media and the growth was noted after one or two days. Minimum inhibitory concentration is the lowest concentration, which showed no microbes growth after spot subculture for each drug. The test mixture should contain 100 µg/mL

Here, in represent case for evaluating antibacterial activity, the bacterial strains *viz*. *Staphylococcus aureus* MTCC 96 and *Bacillus subtilis* MTCC 441 (Gram-positive); *Escherichia coli* MTCC 443 and *Salmonella typhimurium* MTCC 98 (Gram-negative) were selected. The strains were procured from the department of microbiology, R K University, Rajkot, India.

Antifungal assay: The newly prepared compounds were screened for their antifungal activity as primary screens in six sets against *C. albicans*, *A. niger* and *A. clavatus* at various concentrations of 1000, 500 and 250 µg/mL. The primary active compounds were similarly diluted to obtain 200 and 100 µg/mL concentrations for secondary screening to test in the second set of dilutions against all fungi. Each compound's fungal activity was compared with nystatin as a standard drug, which showed 100, 100 and 100 µg/mL MIC against *C. albicans*, *A. niger* and *A. clavatus*, respectively.

In present case evaluation of antifungal activity, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323 as fungal strains were selected. The strains were procured from the department of microbiology, R K University, Rajkot, India.

Synthesis of thiazolidine-2,4-dione (I): In 100 mL dry round bottom flask containing 2-chloroacetic acid (5 g, 53 mmol) and thiourea (4 g, 53 mmol), added 30 mL deionized water to dissolve them. Stirred the resulting solution for 10 min at room temperature till it becomes cleared and then added conc. HCl (5 mL) in to the solution in dropwise. Place the round bottom flask on oil bath to refluxed temperature for 10 h. Monitor the reaction by TLC using hexane:ethyl acetate (7:3 mL) as solvent system. After the completion cooled the reaction mixture on ice-bath, flirted the shiny crystal that formed subsequently on cooling and washed with cooled water to afford white shiny crystal as thiazolidine-2-4-dione (**I**) (m.f.: $C_3H_3NO_2S$; m.p.: 123-125 ºC; 5.5 g, 90% yield, white crystal).

Synthesis of (*E*)-5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (II): In a 250 mL three necked flask equipped with Dean-stark apparatus, added thiazolidine-2-4-dione (**I**) (5 g, 43 mmol), 4-hydroxy benzaldehyde (5.26 g, 43 mmol) and dry toluene (20 mL), stirred the resultant mixture to form a clear solution. Then added dry piperidine in catalytic amount (0.5 mL) and refluxed the reaction mixture at 110 ºC, separate the water, which generates during reaction. After completion of reaction (checked by TLC using hexane:ethyl acetate (7:3 mL) solvent system) cooled it, separated yellow solid and filtered, washed with cooled toluene and dry ethanol to afford pure product as (*E*)-5-(4-hydroxybenzylidene)thiazolidine-2,4-dione **(II)** (m.f.: $C_{10}H_7NO_3S$; m.p.: 303-304 ºC; 7 g, 73% yield, Yellow solid).

Synthesis of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (III): (*E*)-5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (**II**)

(3 g, 13 mmol) in 50 mL dry stainless steel laboratory autoclave (catalytic hydrogenation apparatus), added 20 mL of HPLC grade methanol and to dissolve the solid. Then added 10% Pd/C (wet) (3 g) to the solution and purged the hydrogen gas up to 250 psi, tight autoclave and put on hot plate with magnetic stirrer at 70 ºC for 5 h. After completion of reaction indicate by TLC using hexane:ethyl acetate (8:2 mL solvent system), released excess hydrogen gas in open air and transfer the solution in to glass beaker, followed by filter on high flow clay pad to remove Pd/C catalyst. The filtrate was concentrate under reduced pressure to formed greenish coloured semi-solid, added diethyl ether and triturate, filtered the solid and washed with cooled ether, dried it to get pure **III** (m.f.: $C_{10}H_9NO_3S$; 80% yield, Greenish solid).

Synthesis of 5-(4-((4-bromobenzyl)oxy)benzyl)thiazolidine-2,4-dione (IV): Dissolved 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (**III**) (2 g, 9 mmol) in 100 mL dry round bottom flask containing dry DMF (20 mL). Then cooled to 0-5 ºC using ice-bath, add 4-bromo benzyl bromide (2.7 g, 10.8 mmol) and sodium bicarbonate (2.3 g, 27 mmol). Stirred the solution at room temperature for 12 h. The reaction was monitored by using TLC with hexane:ethyl acetate (7:3) solvent system. After completion poured the reaction mixture into a crushed ice with stirring, added ethyl acetate to extract the product, separate the organic layer and washed with brine solution twice and dried it on anhydrous sodium sulphate. Concentrated the solution under reduced pressure to get residue, added hexane with trituration to remove excess of 4-bromo benzyl bromide, filtered the solid, washed with hexane and dried it to get **IV** (m.f.: $C_{17}H_{14}BrNO_3S$; 90% yield, white solid) (**Scheme-I**).

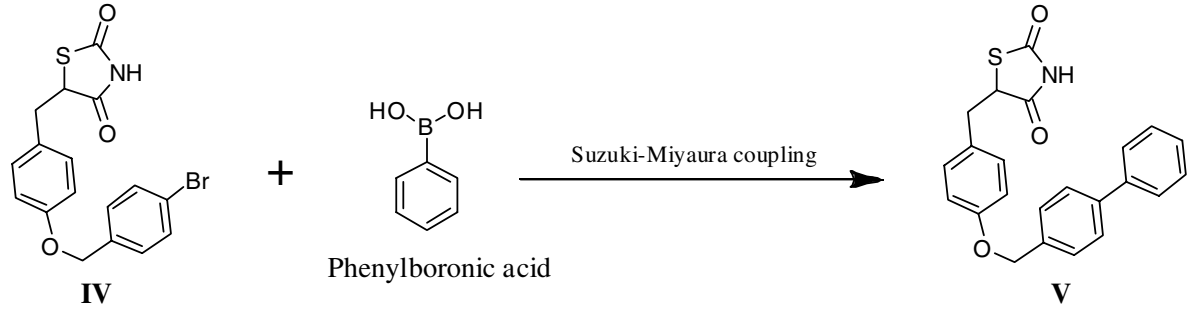
General procedure (Suzuki coupling) for synthesis of 5-(4-(Substituted-[1,1′-biphenyl]-4-ylmethoxy)benzyl)thiazolidine-2,4-diones (V-XVI)

Microwave irradiation (MW) method: Prepare a solvent mixture of toluene (5 mL), ethanol (0.5 mL) and distilled water (0.5 mL) in standard 10 mL dry borosilicate glass microwave vial sealed with PTFE-coated silicon septum, stirred to mix it. Then added 5-(4-((4-bromobenzyl)oxy)benzyl)thiazolidine-2,4-dione (**IV**) (500 mg, 1.3 mmol), substituted aryl boronic acid (1.95 mmol), K_2CO_3 (450 mg, 3.25 mmol) and degassed the solution by purging of N_2 gas for 15 min, the solution turns to light yellow coloured followed by the addition of $[Pd[P(Ph_3)]_4]$ (150 mg, 0.1%) as catalyst and sealed the vial, solution turns to light brown coloured. Put the vial in silicon carbide vessels in microwave at 110 ºC for 6 min. After completion (checked by TLC using ethyl acetate:hexane (3:7 mL) solvent system), poured the reaction mixture into crushed ice and extracted the product in ethyl acetate (3 × 15 mL). Separated the organic layer and washed with brine and dried it on anhydrous sodium sulphate, concentrated in vacuum to get brown coloured residue. Purified the final product was using column chromatography 10% ethyl acetate:hexane eluent system to get pure thiazolidinediones derivatives (**V-XVI**).

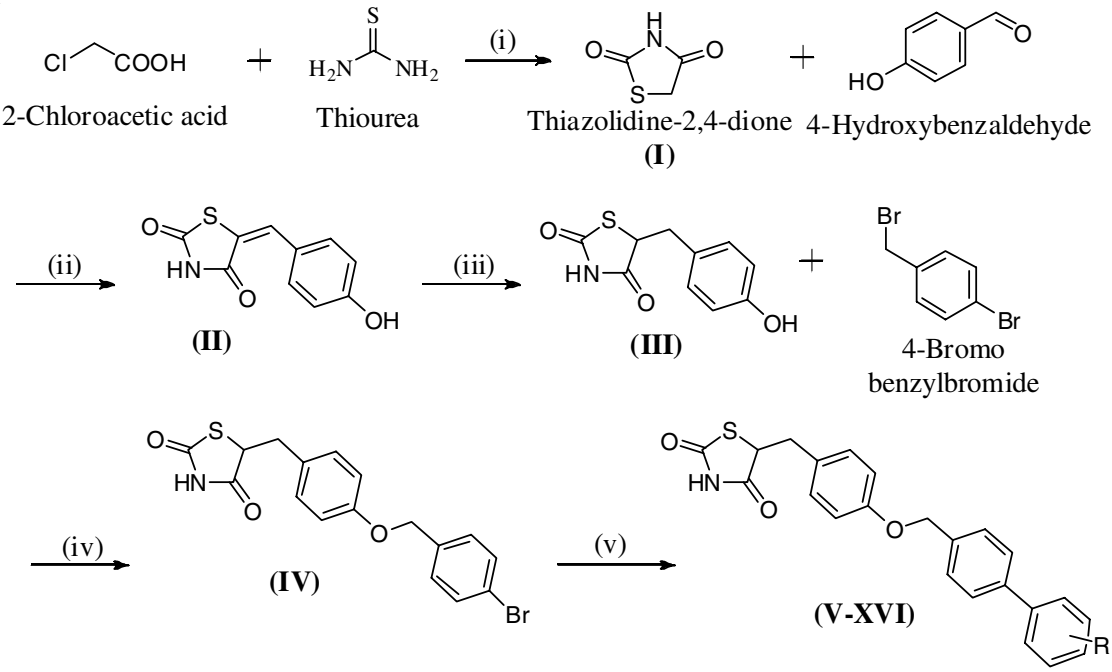
Conventional heating (CH) method: Prepared a solvent mixture of toluene (5 mL), ethanol (0.5 mL) and distilled water (0.5 mL) in vial, stirred to mix it. Then added 5-(4-((4-bromobenzyl)oxy)benzyl)thiazolidine-2,4-dione (**IV**) (500 mg, 1.3 mmol), substituted aryl boronic acid (1.95 mmol), K_2CO_3 (450 mg, 3.25 mmol) and degassed the solution by purging of N_2 gas for 15 min, the solution turns to light yellow coloured. Followed b the addition of $[Pd[P(Ph_3)]_4]$ (150 mg, 0.1%) as catalyst and sealed the vial, solution turns to light brown coloured. The mixture was stirred and heated to 110 ºC for 60 min. After completion (checked by TLC using ethyl acetate: hexane (3:7 mL) solvent system), poured the reaction mixture into crushed ice and extract the product in ethyl acetate (3 × 15 mL). Separated the organic layer and washed with brine and dried it on anhydrous sodium sulphate, concentrated in vacuum to get brown coloured residue. Purified the final product was using column chromatography 10% ethyl acetate:hexane eluent system to get pure thiazolidinediones derivatives (**V-XVI**) (**Scheme-II**).

5-(4-((4′-Methoxy-[1,1′-biphenyl]-4-yl)methoxy)-benzyl)thiazolidine-2,4-dione (V): White solid; yield: MW = 90%, CH = 69%; m.p.: 106-108 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 3.09-3.21 (m, 2H, -CH_2 (A)), 3.79 (s, 3H (B), -OCH_3), 4.58-4.71 (dd, 2H, -CH_2 (C), J = 14.8, 36.4 Hz), 4.99 (s, 1H, -CH (D)), 6.67-6.69 (d, 2H (E), Ar-H, J = 10.4 Hz), 7.01-7.09 (m, 6H (F), Ar-H), 7.51-7.59 (m, 4H (G), Ar-H), 9.42 (s, 1H (H), -NH-); ^{13}C NMR (101 MHz, DMSO-d_6): δ 35.8 (C1), 43.98 (C2), 51.25 (C3), 55.12 (C4), 114.3 (C5), 115.16 (C6), 125.93 (C7), 126.22 (C8), 127.71 (C9), 130.6 (C10), 132.03 (C11), 133.68 (C12), 139.10 (C13), 156.52 (C14), 158.91 (C15), 171.10 (C16), 173.79 (C17); IR (KBr, ν_{max}, cm^{-1}): 3414 (N-H *str.*, *sec*. cyclic imide (m)), 3010. 2914 (C-H, *str.*, aromatic), 2843 (C-H, *str.*, alkane), 1757, 1678 (C=O, *str.*, 5-membered cyclic imide), 1608, 1500, 1448 (C=C, *str.*, aromatic), 1384 (C-H, bend.), 1153 (C-S, *str.*), 976 (*p*-subs. benzene ring); Mass (*m/z*): Exact mass: 419, Found mass: 419.

4′-((4-((2,4-Dioxothiazolidin-5-yl)methyl)phenoxy)-methyl)-[1,1′-biphenyl]-4-carbonitrile (VI): White solid;



Scheme-I: Suzuki-Miyaura coupling of **IV** with phenyl boronic acid



Scheme-II

Yield: MW = 78%, CH = 65%; m.p.: 108-110 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.14-3.30 (m, 2H, -CH_2 (A)), 4.61-4.74 (q, 2H, -CH_2 (B)), 4.99-5.02 (q, 1H, -CH (C)), 6.66-6.68 (d, 2H (D), Ar-H, J_{DE} = 8 Hz), 7.01-7.03 (d, 2H (E), Ar-H, J_{ED} = 8 Hz), 7.12-7.14 (d, 2H (F), Ar-H, J_{FG} = 8 Hz), 7.65-7.67 (d, 2H (G), J_{GF} = 8 Hz), 7.85-7.87 (d, 2H (H), J_{HI} = 8 Hz), 7.93-7.95 (d, 2H (I), J_{IH} = 8 Hz), 9.41 (s, 1H (J), -NH-); ^{13}C NMR (101 MH_Z, DMSO-d_6): δ 35.2, 56.76, 70.08, 110.5, 115.2, 117.6, 125.22, 130.5, 131.06, 135.12, 143.02, 155.15, 172.04, 174.67; IR (KBr, ν_{max}, cm^{-1}): 3377 (N-H *str.*, *sec*. cyclic imide (m)), 3016 (C-H, *str.*, aromatic), 2922 (C-H, *str.*, alkane), 2231 (-CN *str.*), 1743, 1674 (C=O, *str.*, 5-member cyclic imide), 1606, 1514, 1446 (C=C, *str.*, aromatic), 1354 (C-H, bend.), 1220 (C-O *str.*), 1153 (C-S, *str.*), 976 (*p*-subs. benzene ring); Mass (*m/z*): Exact mass: 414, Found mass: 414.

5-(4-([1,1′-Biphenyl]-4-ylmethoxy)benzyl)thiazolidine-2,4-dione (VII): White solid; Yield: MW = 82%, CH = 70%; m.p.: 154-156 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.10-3.31 (m, 2H, -CH_2 (A)), 4.60-4.73 (q, 2H, -CH_2 (B)), 5.0 (d, 1H, -CH (C), J_{CA} = 2.8 Hz), 6.67-6.69 (d, 2H (D), Ar-H, J_{DE} = 8 Hz), 6.93-7.03 (dd, 4H (E), Ar-H, J_{ED} = 7.6, 30.8 Hz), 7.37 (d, 1H (F), Ar-H, J_{FH} = 7.2 Hz), 7.45-7.48 (t, 2H (G), Ar-H, J_{GE} = 7.6 Hz), 7.56-7.58 (d, 2H (H), Ar-H, J_{HI} = 8 Hz), 7.63-7.65 (d, 2H (I), Ar-H, J_{IH} = 8 Hz), 9.42 (s, 1H, -NH-); ^{13}C NMR (101 MHz, DMSO-d_6): δ 35.84 (C1), 43.96 (C2), 51.25 (C3), 115.16 (C4), 125.91 (C5), 126.76 (C6), 127.47 (C7), 127.77 (C8), 128.91 (C9), 130.62 (C10), 134.46 (C11), 139.71 (C12), 139.71 (C13), 156.52 (C14), 171.12 (C15), 173.80 (C16); IR (KBr, ν_{max}, cm^{-1}): 3383 (N-H *str.*, *sec.* cyclic imide (m)), 3030 (C-H, *str.*, aromatic), 2922 (C-H, *str.*, alkane), 1739, 1668 (C=O, *str.*, 5-member cyclic imide), 1612, 1591, 1514, 1433 (C=C, *str.*, aromatic), 1394 (C-H, bend.), 1269 (C-O, *str.*), 1149 (C-S, *str.*), 969 (*p*-subs. benzene ring); Mass (*m/z*): Exact mass: 389.47, Found mass: 389.

5-(4-((4′-Fluoro-[1,1′-biphenyl]-4-yl)methoxy)benzyl)-thiazolidine-2,4-dione (VIII): White solid; Yield: MW = 84%, CH = 72%, m.p.: 111-113 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.01-3.07 (dd, 1H, -CH_2, J = 8.4, 14 Hz), 3.26-3.31 (dd, 1H, -CH_2, J = 3.6, 14 Hz), 4.36-4.39 (dd, 1H, -CH, J = 3.6, 8.4 Hz), 4.60-4.68 (q, 2H, -CH_2), 4.88 (s, 1H, -NH-C=O), 6.58-6.60 (d, 2H, Ar-H, J = 8 Hz), 6.94-6.96 (d, 2H, J = 8 Hz), 7.03-7.07 (t, 2H, J = 8.4 Hz), 7.18-7.22 (t, 2H, Ar-H, J = 8 Hz), 7.37-7.47 (m, 4H, Ar-H); ^{13}C NMR (101 MH_Z, DMSO-d_6): 37.44, 44.83, 51.59, 115.53, 115.84, 127.23, 128.68, 130.76, 133.96, 136.68, 140.02, 155.02, 161.34, 163.79, 171.06, 173.74; IR (KBr, ν_{max}, cm^{-1}): 3408 (N-H *str.*, *sec*. cyclic imide (m)), 3319 (C-H, *str.*, aromatic), 1751, 1654 (C=O, *str.*, 5-membered cyclic imide), 1492 (C-H, bend., 1259 (C-O, *str.*), 1093 (C-S, *str.*), 804 (*p*-subs. benzene ring); Mass (*m/z*): Exact mass: 407, Found mass: 407.

5-(4-((3′,4′,5′-Trifluoro-[1,1′-biphenyl]-4-yl)methoxy)-benzyl)thiazolidine-2,4-dione (X): Yellow solid; Yield: MW = 78%, CH = 65%, m.p.: 127-129 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.13-3.85 (q, 2H, -CH_2), 4.61-4.73 (dd, 2H, -CH_2, J = 15.2, 32.4 Hz), 5.01 (s, 1H, -CH), 6.68 (s, 2H, Ar-H), 7.01-7.12 (t, 4H, Ar-H), 7.64 (s, 4H, Ar-H), 9.43 (s, 1H, -NH-C=O); ^{13}C NMR (101 MH_Z, DMSO-d_6): δ 28.96, 35.82, 43.83, 51.24, 111.19, 115.15, 125.84, 126.87, 127.82, 128.25, 130.61, 136.08, 137, 139, 149, 151.75, 156.50, 171.11, 173.75; IR (KBr, ν_{max}, cm^{-1}) 3485 (N-H *str.*, secondary cyclic imide (m)), 3441 (C-H, *str.*, aromatic), 3055, 2960 (C-H, *str.*, alkane), 1747, 1651 (C=O, *str.*, 5-member cyclic imide), 1533 (C=C, *str.*, aromatic), 1332 (C-H, bend., 1259 (C-O, *str.*), 1037 (C-S, *str.*), 800 (*p*-subs. benzene ring); Mass (*m/z*): Exact mass: 443, Found mass: 443.

5-(4-((3′-Amino-[1,1′-biphenyl]-4-yl)methoxy)benzyl)-thiazolidine-2,4-dione (XI): Grey solid; Yield: MW = 76%, CH = 62%, m.p.: 129-131 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.06-3.14 (q, 1H, -CH_2 (A)), 3.27-3.39 (dd, 1H, -CH_2 (A), J_{AC} = 4, 14 Hz), 4.58-4.71 (q, 2H (B), -CH_2), 4.96-5.01 (dd, 1H, -CH (C), J_{CA} = 4.4, 16 Hz), 5.17 (s, 2H (D), -NH_2), 6.55-6.58 (dd, 1H (E), Ar-H, J_{EH} = 1.2, J_{EJ} = 8 Hz), 6.67-6.69 (d, 2H (F), Ar-H, J_{FI} = 8 Hz), 6.74-6.76 (d, 1H (G), Ar-H, J_{GH} = 8 Hz), 6.80-6.81 (t, 1H (H), Ar-H, J_{HJ} = 2 Hz), 7.01-7.03 (d, 2H (I),

J_{IF} = 8 Hz), 7.08-7.12 (m, Ar-H, 3H (J)), 7.48-7.51 (d, 2H (K), J_{KJ} = 12 Hz), 9.41 (s, 1H (L), -NH-); 13C NMR (101 MHZ, DMSO-d_6): δ 35.89 (C1), 44.00 (C2), 51.27 (C3), 112 (C4), 113.19 (C5), 114.33 (C6), 115.04 (C7), 125.99 (C8), 126.52 (C9), 129.38 (C10), 130.01 (C11), 132.03 (C12), 134.07 (C13), 140.38 (C14), 140.44 (C15), 149.06 (C16), 156.50 (C17), 171.12 (C18), 173.82 (C19); IR (KBr, ν_{max}, cm^{-1}): 3338 (N-H, *str.* amine), 3305 (N-H *str.*, *sec*. cyclic imide (m)), 1747, 1681 (C=O, *str.*, 5-membered cyclic imide), 1516 (C=C, *str.*, aromatic), 771 (*m*-subs. benzene ring); Mass (*m/z*): Exact mass: 404, Found mass: 404.

5-(4-((3′-Fluoro-[1,1′-biphenyl]-4-yl)methoxy)benzyl)-thiazolidine-2,4-dione (XIII): White solid; Yield: MW = 80%, CH = 69%, m.p.: 110-112 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.10-3.31 (qq, 2H, -CH_2), 4.61-4.74 (q, 2H, -CH_2), 4.99-5.02 (q, 1H, -CH), 6.67-6.69 (d, 2H, Ar-H, *J* = 8 Hz), 7.01-7.11 (dd, 4H, Ar-H, *J* = 8 Hz), 7.20-7.21 (t, 1H, Ar-H), 7.49-7.51 (d, 3H, *J* = 8 Hz), 7.61-7.63 (d, 2H, Ar-H, *J* = 8 Hz), 9.43 (s, 1H, -NH-); ^{13}C NMR (101 MH_Z, DMSO-d_6): δ 35.82, 43.91, 51.25, 113.43, 114.28, 115.16, 122.71, 125.86, 126.88, 127.80, 130.79, 135.13, 137.98, 142.19, 156.52, 161.45, 163.87, 171.12, 173.77; IR (KBr, ν_{max}, cm^{-1}3441 (N-H *str.*, *sec*. cyclic imide (m)), 3352 (C-H, *str.*, aromatic), 2964 (C-H, *str.*, alkane), 1749, 1662 (C=O, *str.*, 5-membered cyclic imide), 1591, 1502 (C=C, *str.*, aromatic), 1334, 1261 (C-H bend., 1222 (C-O, *str.*), 1101 (C-S, *str.*), 804 (*p*-subs. benzene ring); Mass (*m/z*): Exact mass: 407, Found mass: 407.

5-(4-((2′,4′-Dichloro-[1,1′-biphenyl]-4-yl)methoxy)-benzyl)thiazolidine-2,4-dione (XV): Light green solid; Yield: MW = 79%, CH = 66%, m.p.: 97-99 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.15-3.38 (t, 2H, -CH_2, *J* = 30 Hz), 4.67-4.71 (d, 2H, -CH_2, *J* = 16 Hz), 5.02 (s, 1H, -CH), 6.08 (s, 2H, Ar-H), 7.03-7.50 (m, 8H, Ar-H), 7.73 (s, 1H, Ar-H), 9.39 (s, 1H, -NH-C=O); ^{13}C NMR (101 MH_Z, DMSO-d_6): 35.84, 43.95, 51.31, 115.16, 125.90, 127.03, 127.62, 129.27, 130.60, 132.32, 132.94, 135.13, 136.76, 138.28, 156.50, 171.14, 173.82.; IR (KBr, ν_{max}, cm^{-1}) 3369 (N-H *str.*, *sec*. cyclic imide (m)), 3304 (C-H, *str.*, aromatic), 2845 (C-H, *str.*, alkane), 1747, 1678 (C=O, *str.*, 5-membered cyclic imide), 1612-1514 (C=C, *str.*, aromatic), 1381-1334 (C-H bend., 1219 (C-O, *str.*), 1141 (C-S, *str.*), 968, 806, 769 (1,2,4-trisubs. benzene ring); Mass (*m/z*): Exact mass: 458, Found mass: 458.

5-(4-((4′-Ethyl-[1,1′-biphenyl]-4-yl)methoxy)benzyl)-thiazolidine-2,4-dione (XVI): Light yellow solid; Yield: MW = 90%, CH = 75%, m.p.: 109-111 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29-1.33 (t, 3H, -CH_3, *J* = 8 Hz), 2.70-2.75 (q, 2H, -CH_2), 3.11-3.16 (q, 1H, -CH_2), 3.35-3.39 (dd, 1H, -CH_2, *J* = 3.2, 14 Hz), 4.44-4.47 (q, 1H, -CH), 4.71-4.80 (q, 2H, -CH_2), 5.91 (s, 1H, -NH-), 6.69-6.71 (d, 2H, Ar-H, *J* = 12 Hz), 7.02-7.04 (d, 2H, Ar-H, *J* = 12 Hz), 7.30-7.32 (d, 4H, Ar-H, *J* = 8 Hz), 7.54-7.56 (d, 4H, Ar-H, *J* = 7.6 Hz); ^{13}C NMR (101 MH_Z, DMSO-d_6): 15.16, 28.54, 37.39, 44.95, 51.68, 115.61, 127.22, 128.74, 130.75, 133.58, 137.89, 140.93, 143.71, 155.31, 171.50, 174.02; IR (KBr, ν_{max}, cm^{-1}) 3338 (N-H *str.*, *sec*. cyclic imide (m), 1747, 1678 (C=O, *str.*, 5-membered cyclic imide), 1514 (C=C, *str.*, aromatic), 1386, 1382 (C-H bend., 1219 (C-O, *str.*), 1151 (C-S, *str.*), 970 (*p*-subs. benzene ring); Mass (*m/z*): Exact mass: 417, Found mass: 417.

RESULTS AND DISCUSSION

In present work, some new 5-substituted thiazolidine-dione's derivatives were synthesized. The main nucleus of compounds is a thiazolidinedione's, which is formed by cyclization between thiourea and chloroacetic acid. Thiazolidine-2,4-diones possess an active methylene group, so both hydrogen atom easily replace with oxygen of benzaldehyde to get exo-cyclic double bond on ring. Which on further alkylation on hydroxyl group to get the product as a scaffold. The free bromine undergoes Suzuki-miyaura coupling with phenyl boronic acid to afforded series of new 5-substituted thiazolidinedione's derivatives (**V-XVI**).

The first step of **Scheme-I** is the synthesis of thiazolidine-2,4-dione **(I)**, which is heterocyclic nucleus in target molecule. In thiazolidinedione's the 5th membered in ring is methylene group *i.e.* –CH_2, which behaves as an active methylene because of presence of neighbouring carbonyl and highly electronegative sulphur atom. Both hydrogens are easily replaced by aryl aldehyde (aldol type reaction) in base catalyst. Compound **II** was synthesized by this phenomenon. In third step, the exocyclic double bond on thiazolidinedione's was reduced by the catalytic hydrogenation by using autoclave to afford 5-(4-hydroxybenzyl)-thiazolidine-2,4-dione **(III)**. Followed by the alkylation of hydroxyl group by 4-bromobenzyl bromide under basic condition to give 5-(4-((4-bromobenzyl)oxy)benzyl)-thiazolidine-2,4-dione **(IV)**, which is a scaffold for both series. In final step of scheme one is an microwave assisted suzuki-miyaura coupling of compound **IV** with substituted aryl boronic acid using Pd complex catalyst to got final molecules as 5-(4-(substituted [1,1′-biphenyl]-4-ylmethoxy)benzyl)thiazolidine-2,4-diones **(V-XVI)**.

Reaction optimization: Table-1 shows the number of experiments which were performed for optimizing the reaction condition by changing solvents ratio, bases, catalyst, temperature with time. Different reaction conditions were optimized like room temperature, ultrasonic reflux and microwave conditions. It was observed that microwave conditions are better compared to other conditions. The solvents used were toluene, water, ethanol, isopropyl alcohol, DMM and dioxane with binary mixture of two or more solvents by keeping water constant. The base catalysts were K_2CO_3, Na_2CO_3 and Cs_2CO_3 used, in some experiments TBAB was also added as phase transfer catalyst. Amongst all experiments, entry-8 (Table-1) gives maximum yield by using solvent mixture toluene:water:ethanol (5:0.5:0.5 mL), K_2CO_3 as base and $Pd(PPh_3)_4$ as catalyst at 110 ºC for 6 min in microwave irradiated to afford 90% of yield.

All the synthesized compounds were characterized by various spectrometric techniques like ^{1}H NMR, ^{13}C NMR, IR, as well as mass spectroscopy. The data obtained are very well supported to final molecules. In ^{1}H NMR shows very sharp peak at most probable chemical shift value (δ ppm). Due to chirality in molecule the methylene proton non-equivalency are proved by ^{1}H NMR. Some characteristic peaks in ^{1}H NMR between 9 to 10 δ ppm shows an -NH- (cyclic amidic proton), also in some spectra the disappearance of –NH- proton by deuterium labeling is one of the major evidence towards the

TABLE-1
OPTIMIZATION TABLE FOR COMPOUND **V**[a]

Entry	Solvent	Base	Catalyst	Condition	Temp. (°C)	Time (min)	Yield[b] (%)
1	Toluene:water (9:1 mL)	Na_2CO_3	$Pd(PPh_3)_4$	RT	110	80	52
2	Toluene:water:ethanol (9:0.5:0.5 mL)	K_2CO_3	$Pd(PPh_3)_4$	Reflux	110	60	68
3	THF:water (9:1 mL)	Na_2CO_3	$PdCl_2(PPh_3)_2$	Ultrasonic	65	45	72
4	Toluene:water (9.5:0.5 mL)	Na_2CO_3 + TBAB	$Pd(PPh_3)_4$	Microwave[a]	105	10	80
5	IPA:water (9:1 mL)	K_2CO_3	$Pd(OAc)_2 + PPh_3$	RT	80	80	64
6	DMM:water (9:1 mL)	Na_2CO_3	$PdCl_2(PPh_3)_2$	Reflux	60	60	80
7	Dioxane:water (9:1 mL)	Cs_2CO_3	$Pd_2(dba)_3$	Ultrasonic	100	45	82
8	Toluene:water:ethanol (9:0.5:0.5 mL)	K_2CO_3	$Pd(PPh_3)_4$	Microwave[a]	110	6	90
9	DMM:water (9:1 mL)	Cs_2CO_3 + TBAB	$PdCl_2(PPh_3)_2 + PPh_3$	Microwave[a]	60	8	78
10	Toluene:water (9:1 mL)	Na_2CO_3	$Pd(PPh_3)_4$	Microwave[a]	110	8	65

[a]Experiments were performed under Microwave condition, [b]Isolated yield

synthesized molecules. In ^{13}C NMR spectra, two peaks at the highest δ ppm at about 170 for two carbonyl groups. The IR spectra the functional group pattern around 3300 cm^{-1} for -NH-starching frequency, also near 1700 cm^{-1} for carbonyl group. In some compounds, the possible mass fragments also evidence toward formation of targeted compounds (Table-2).

Biological evaluation

Antibacterial activity: The MIC values of all the synthesized compounds **(V-XVI)** and standard drugs against selected microbes are presented in Table-3. The result revealed that some synthesized compounds were much potent towards the bacterial strains as comparised to the standard drugs. The compounds **VI**, **XII** (100 µg/mL) and **VII**, **XVI** (100 µg/mL) were found to be more active against *B. subtillis* with respect to the standard drug ampicillin. Compounds **VII**, **XII** and **XVI** (100 µg/mL) showed an excellent activity against *S. aureus* with respect to standard drugs ampicillin and norfloxacin. Compounds **VI**, **XII** and **XVI** (100 µg/mL) showed more activity against *E. coli* with respect to the standard drugs ciprofloxacin,

TABLE-2
PHYSICAL CONSTANT OF SYNTHESIZED COMPOUNDS (**V-XVI**)

Comp. code	R	m.w. (g/mol)	m.p. (°C)	Yield[a]		Yield[b]	
				%	Time	%	Time
V	4-OCH_3 phenyl	419	106-108	69	60	90	6
VI	4-CN phenyl	414	108-110	65	60	78	8
VII	Phenyl	389	154-156	70	60	82	6
VIII	4-Floro phenyl	407	111-113	72	60	84	10
IX	3-Thienyl	395	131-133	58	60	75	12
X	3,4,5-tri F phenyl	443	127-129	65	60	78	10
XI	3-NH_2	404	129-131	62	60	76	10
XII	3-Bromo phenyl	468	108-110	72	60	84	8
XIII	3-Fluoro phenyl	407	110-112	69	60	80	8
XIV	4-Bromo phenyl	468	94-96	74	60	86	8
XV	2,4-di chloro phenyl	458	97-99	66	60	79	8
XVI	4-Ethyl phenyl	417	109-111	75	60	90	10

CH[a] = Conventional heating method, MW[b] = Microwave irradiation method.
*The m.p. of all synthesized compounds was measured by using open capillary apparatus.

TABLE-3
MIC VALUE OF 5-(4-(SUBSTITUTED-[1,1'-BIPHENYL]-4-YLMETHOXY)BENZYL)THIAZOLIDINE-2,4-DIONES

Compd. No.	Minimum inhibitory concentration (µg/mL)					
	Antibacterial activity				Antifungal activity	
	Gram-positive bacteria		Gram-negative bacteria			
	Bacillus subtillis	*Staphylococcus aureus*	*Escherichia coli*	*Salmonella typhi*	*Aspergillus niger*	*Aspergillus clavatus*
V	500	500	250	250	1000	>1000
VI	100	200	100	100	100	500
VII	100	100	100	200	100	250
VIII	200	500	250	100	200	500
IX	500	250	200	500	500	500
X	500	250	200	500	500	500
XI	250	500	500	250	>1000	500
XII	100	100	200	125	500	500
XIII	500	200	250	250	500	>1000
XIV	250	250	500	500	>1000	500

chloramphenicol and ampicillin. Compounds **VI** and **VIII** showed activity against *S. typhi* with respect to standard drugs ciprofloxacin and chloramphenicol and comparative with respect to standard drug ampicillin.

Antifungal activity: Compounds **VI**, **VII** and **XVI** (100 µg/mL) showed more activity against *A. niger* with respect to standard drug greseofulvin and nystatin. From the obtained results, it can be interpreted that compounds with electron withdrawing group substitution showed more potent activity compared to those possessing electron donating group substitution.

Conclusion

In summary, a one-pot greener protocol is developed to provide a rapid and efficient synthesis of 5-(4-(substituted [1,1′-biphenyl]-4-yl-methoxy) benzyl)thiazolidine-2,4-diones from readily available starting materials like K_2CO_3 as catalyst and solvent mixture toluene:water:ethanol (5:0.5:0.5 mL) to minimize the impurity formation and also to improve the yield of final compounds. The advantages of microwave-assisted synthesis to minimize the reaction time and produced higher yields. The *in vitro* antimicrobial study of newly synthe-sized adducts indicates that compounds **VI**, **VII**, **VIII**, **XII** and **XVI** have shown moderate activity against different microbes.

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