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Microwave-assisted synthesis and evaluation of N-substituted thiazolidine-2,4-dione derivatives as antimicrobial agents

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Abstract

A series of *N*-substituted thiazolidine-2,4-dione derivatives bearing potentially bioactive substituents were synthesized by microwave irradiation method. Structural elucidation was accomplished by ^{1}H NMR, ^{13}C NMR, IR, Mass and elemental analyses. The synthesized compounds were evaluated for antimicrobial activities. Among the compounds studied, compounds **4i** and **4d** showed potent antimicrobial activities.

Keywords: Thiazolidine-2,4-dione, antimicrobial activities, microwave irradiation, N-substituted thiazolidine-2,4-dione

Introduction

Sulfonylureas and metformin are the most common antidiabetic agents that induce severe hypoglycemia and weight gain [1]. In addition, there are increased rates of both primary and secondary failures associated with them [2]. Hence, there is a need for developing insulin resistance upgrading drugs for type 2 diabetes. Troglitazone 50 [3], the first drug on the market failed to survive due to liver toxicity. 2,4-thiazolidinedione class agents, pioglitazone 48 [4] and rosiglitazone 51 [5] are currently in clinical use. Ciglitazone 47 [6] has antihyperglycemic activity in insulin resistant animal models. But, anaemia, edema and body weight gain [7] are associated with 2,4-thiazolidinediones drugs. Drugs with more advanced profile are the focus of attention. Besides, thiazolidine derivatives show anticancer [8], antiinflammatory [9], antiobesity [10], antifungal [11], antidiabetic [12], cardiotonic [13] and anticonvulsant [14] acivities. Multiplicity of biological activities along with antidiabetes has made the study of 2,4-thiazolidinediones interesting.

Pharmaceutical industry requires quick production of novel chemical entities. This short reaction time is offered by microwave-assisted synthesis. Therefore, we utilized the microwave irradiation technique to promote the synthesis of bioactive 2,4-thiazolidinedione derivatives. In continuance to our work on the synthesis of biologically-active heterocycles [15-16], herein we report an efficient microwave-assisted synthesis and antimicrobial activities of a novel series of *N*-substituted thiazolidine-2,4-dione derivatives using CEM Discover microwave synthesizer.

Experimental

Melting points were determined on Thomas Hoover melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer using $CDCl_3$ as solvent. The chemical shifts were expressed in parts per million downfield shifts using tetramethylsilane as internal standard. Infrared (IR) spectra were recorded on Shimadzu 8300 IR spectrometer. Mass spectra were recorded on Shimadzu 2010A LCMS system. Elemental analyses were obtained on a Vario-EL instrument. Thin layer chromatography (TLC) was done with pre-coated silica gel G plates using Toluene-Ethylacetate (7:3) as eluent. All the Microwave irradiation experiments were performed in CEM Discover microwave system.

Thiazolidine-2,4-dione (2)

A mixture of monochloroacetic acid (1.00 g, 10.58 mmol) and thiourea (0.81 g, 10.6 mmol) in water (2 mL) were introduced into CEM Discover microwave reaction vessel. The vessel was sealed and stirred for 1 hour at room temperature. The resulting 2-imino-thiazolidin-4-one 1 was irradiated by 200 Watt microwave at 140°C for 10 min. The mixture was cooled to room temperature and stirred for 1 hr. The formed solid was filtered and recrystallized from hot water to yield 1.10g (90%), m.p. 124-125°C. ^{1}H NMR $CDCl_3$: δ 4.2 (s, 2H, CH_2), 9.1 (bs, 1H, NH). ^{13}C NMR $CDCl_3$: δ 35.9, 168.5, 169.2. IR (KBr pellet, cm^{-1}): n 1241 (-C-N), 1492 (-CH_2), 1666, 1738 (ring –C=O), 3121 (-NH). Anal. Calcd for $C_3H_3NO_2S$: C, 30.76, H, 2.58, N, 11.96%. Found: C, 30.61, H, 2.50, N, 11.88%.

3-(2-Bromo-4, 5-dimethoxy-benzyl) thiazolidine-2, 4-dione (4a): typical procedure

A mixture of thiazolidine-2,4-dione (1.00 g, 8.54 mmol), anhy. K_2CO_3 (1.41 g, 10.21 mmol), 1-bromo-2-bromomethyl-4,5

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dimethoxy-benzene (2.65 g, 8.54 mmol) and dimethylformamide (3 mL) were charged into CEM Discover microwave reaction vessel. The vessel was sealed and inserted into CEM discover microwave instrument and irradiated at 200 Watt for 10 min. After completion of the reaction (TLC toluene-ethylacetate; 7:3), the reaction mass was diluted with 25 mL water and the product was extracted with dichloromethane (25 mL). The extract was washed with water (10 mL) and then dried (Na_2SO_4). The solvent was evaporated and the remaining pale yellow oil was crystallized from ethanol to give 2.48 g 4a as a pale yellow solid with a yield of84%, m.p. 146-148^{0}C. ^{1}H NMR $CDCl_3$: δ 3.53(s, 6H, -OCH_3), 3.92 (s, 2H, -CH_2), 4.89 (s, 2H, -CH_2), 6.88 (s, 1H, ArH), 6.82 (s, 1H, ArH). ^{13}C NMR $CDCl_3$: δ 39.2,42.3, 59.1, 119.4, 127.3, 141.1, 145.2, 148.6, 149.8, 169, 169.4. IR (KBr pellet, cm^{-1}): n 521 (C-Br), 1180 (-C-N), 1451 (-CH_2), 1590 (Aromatic –C=C), 1631, 1742 (ring –C=O). MS: m/z 330 (M^+). Anal. Calcd for $C_{12}H_{12}BrNO_4S$: C, 41.63, H, 3.49, N, 4.05%. Found: C, 41.71, H, 3.40, N, 4.01%. The above procedure was used in all cases.

3-Benzyl thiazolidine-2,4-dione (4b)

It was obtained from thiazolidine-2,4-dione (1.00 g, 8.54 mmol), anhy. K_2CO_3 (1.41 g, 10.21 mmol) and benzyl bromide (1.46 g, 8.54 mmol) as a pale yellow crystalline solid with a yield of 1.50 g (85%), m.p. 116-117^{0}C. ^{1}H NMR $CDCl_3$: δ 3.90 (s, 2H, -CH_2), 4.86 (s, 2H, -CH_2), 7.1-7.22 (m, 5H, ArH). ^{13}C NMR $CDCl_3$: δ 36.5, 51.2, 125.5, 127.2, 128.5, 142.4, 168.1, 168.8. IR (KBr pellet, cm^{-1}): n 1174 (-C-N), 1432 (-CH_2), 1541 (Aromatic –C=C), 1648, 1771 (ring –C=O). Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.95, H, 4.38, N, 6.76%. Found: C, 57.90, H, 4.31, N, 6.69%.

3-(6-Methylbenzo[1,3]dioxo-5-yl-methyl)thiazolidine-2, 4-dione (4c)

It was obtained from thiazolidine-2,4-dione (1.00 g, 8.54 mmol), anhy. K_2CO_3 (1.41 g, 10.21 mmol) and 5-clorometyl-6-methyl-benzo [1,3] dioxole (1.58 g, 8.54 mmol) as a pale yellow crystalline solid with a yield of 1.88 g (83%), m.p. 194-195^{0}C. ^{1}H NMR $CDCl_3$: δ 2.38 (s, 3H, -CH_3), 3.92 (s, 2H, -CH_2), 4.94 (s, 2H, -CH_2), 5.82 (s, 2H, -CH_2), 6.81 (s, 1H, ArH), 6.93 (s, 1H, ArH). ^{13}C NMR $CDCl_3$: δ 13.6, 36.8, 44.4, 88.8, 114.1, 115.1, 129.1, 135.5, 144.1, 145.8, 169, 169.9. IR (KBr pellet, cm^{-1}): n 1113 (O-C-O), 1231 (-C-N), 1392 (-CH_2), 1542 (Aromatic –C=C), 1647, 1753 (ring –C=O), 2904 (-CH_3). Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33, H, 4.18, N, 5.28%. Found: C, 54.21, H, 4.11, N, 5.20%.

3-(4-nitrobenzyl)thiazolide-2,4-dione (4d)

It was obtained from thiazolidine-2,4-dione (1.00 g, 8.54 mmol), anhy. K_2CO_3 (1.41 g, 10.21 mmol) and 4-nitro-benzyl bromide (1.85 g, 8.54 mmol) as a pale yellow crystalline solid with a yield of 1.85 g (86%), m.p. 163-164^{0}C. ^{1}H NMR $CDCl_3$: δ 3.93 (s, 2H, -CH_2), 4.89 (s, 2H, -CH_2), 7.41 (d, 2H, ArH), 8.01 (d,2H, ArH). ^{13}C NMR $CDCl_3$: δ 37.1, 50.9, 124.1, 128.2, 144.9, 147.6, 168.6, 169.3 . IR (KBr pellet, cm^{-1}): n 1210 (-C-N), 1447 (-CH_2), 1495 (-NO_2), 1558 (Aromatic –C=C), 1651, 1763 (ring –C=O). Anal. Calcd for $C_{10}H_8N_2O_4S$: C, 47.62, H, 3.20, N, 11.11%. Found: C, 47.51, H, 3.15, N, 11.01%.

4^1-(2,4-Dioxo-thiazolidine-3-ylmethyl) biphenyl-2-carbonitrile (4e)

It was obtained from thiazolidine-2,4-dione (1.00 g, 8.54 mmol), anhy. K_2CO_3 (1.41 g, 10.21 mmol) and 4^1-bromomethyl-biphenyl-2-carbonitrile (2.33 g, 8.54 mmol) as a pale yellow crystalline solid with a yield of 2.29 g (87%), m.p. 134-136^{0}C. ^{1}H NMR $CDCl_3$: δ 3.87 (s, 2H, -CH_2), 4.93 (s, 2H, -CH_2), 7.22 (d, 2H, ArH), 7.31 (d, 2H, ArH), 7.4-7.7 (m, 4H, ArH). ^{13}C NMR $CDCl_3$: δ 38.2, 51.0, 117.1, 120, 126.8, 127.3, 128.3, 128.6, 130.9, 133.1, 133.8, 141.1, 142, 168, 168.6. IR (KBr pellet, cm^{-1}): n 1244 (-C-N), 1458 (-CH_2), 1524 (Aromatic –C=C), 1642 (-CN), 1649, 1761 (ring –C=O). Anal. Calcd for $C_{17}H_{12}N_2O_2S$: C, 66.22, H, 3.92, N, 9.08%. Found: C, 66.29, H, 3.80, N, 8.98%.

4^1-(2,4-Dioxo-thiazolidine-3-ylmethyl)biphenyl-2-carboxylic acid methyl ester (4f)

It was obtained from thiazolidine-2,4-dione (1.00 g, 8.54 mmol), anhy. K_2CO_3 (1.41 g, 10.21 mmol) and 4^1-bromomethyl-biphenyl-2-carboxylic acid methyl ester (2.61 g, 8.54 mmol) as a pale yellow crystalline solid with a yield of 2.36 g (81%), m.p. 198-200^{0}C. ^{1}H NMR $CDCl_3$: δ 3.42 (s, 3H, -OCH_3), 3.89 (s, 2H, -CH_2), 4.89 (s, 2H, -CH_2), 7.19 (d, 2H, ArH), 7.42-7.61 (m, 4H, ArH), 7.95 (d, 2H, ArH). ^{13}C NMR $CDCl_3$: δ 37.5, 50.2, 53.8, 127.2, 127.4, 127.9, 128.8, 130.2, 131, 134.5, 134.8, 139, 140.6, 168.1, 169.1, 169.5. IR (KBr pellet, cm^{-1}): n 1211 (-C-N), 1454 (-CH_2), 1509 (Aromatic –C=C), 1645, 1742 (ring –C=O), 1780 (Ketone –C=O), 2833 (Ketone –CH_3). Anal. Calcd for $C_{18}H_{15}NO_4S$: C, 63.33, H, 4.43, N, 4.10%. Found: C, 63.22, H, 4.34, N, 4.01%.

3-(2-Oxo-2-phenyl-ethyl)-thiazolidine-2,4-dione (4g)

It was obtained from thiazolidine-2,4-dione (1.00 g, 8.54 mmol), anhy. K_2CO_3 (1.41 g, 10.21 mmol) and phenacyl bromide (1.70 g, 8.54 mmol) as a pale yellow crystalline solid with a yield of 1.68 g (84%), m.p. 101-102^{0}C. ^{1}H NMR $CDCl_3$: δ 3.88 (s, 2H, -CH_2), 4.88 (s, 2H, -CH_2), 7.42-7.84 (m, 5H, ArH). ^{13}C NMR $CDCl_3$: δ 37.5, 52.0, 128.2, 128.5, 131.3, 138.1, 165.9 , 167.8, 197.2. IR (KBr pellet, cm^{-1}): n 1241 (-C-N), 1461 (-CH_2), 1511 (Aromatic –C=C), 1638, 1734 (ring –C=O), 1741 (Acyl –C=O), 2741 (Acyl –CH_2). Anal. Calcd for $C_{11}H_9NO_3S$: C, 56.16, H, 3.86, N, 5.95%. Found: C, 56.07, H, 3.81, N, 6.01%.

3-[2-(4-Nitrophenyl)-2-oxo-ethyl]-thiazolidine-2, 4-dione (4h)

It was obtained from thiazolidine-2,4-dione (1.00 g, 8.54 mmol), anhy. K_2CO_3 (1.41 g, 10.21 mmol) and 4-nitro phenacyl bromide (2.09 g, 8.54 mmol) as a pale yellow crystalline solid with a yield of 1.53 g (84%), m.p. 73-74^{0}C. ^{1}H NMR $CDCl_3$: δ 3.88 (s, 2H, -CH_2), 4.89 (s, 2H, -CH_2), 7.99 (d, 2H, ArH), 8.12 (d, 2H, ArH). ^{13}C NMR $CDCl_3$: δ 38.2, 52.3 , 123.5 , 128.8 , 144.4 , 152.9, 166.2, 168.3, 197.1. IR (KBr pellet, cm^{-1}): n 1276 (-C-N), 1431 (-CH_2), 1488 (-NO_2), 1566 (Aromatic –C=C), 1638, 1761

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(ring –C=O), 1777 (Acyl –C=O), 2699 (Acyl –CH_2). Anal. Calcd for $C_{11}H_8N_2O_5S$: C, 47.14, H, 2.88, N, 10.0%. Found: C, 47.03, H, 2.80, N, 9.90%.

3-(4-Fluorobenzyl) thiazolidine-2,4-dione (4i)

It was obtained from thiazolidine-2,4-dione (1.00 g, 8.54 mmol), anhy. K_2CO_3 (1.41 g, 6.52mmol) and 4-fluro benzyl bromide (0.78 g, 5.37 mmol) as a pale yellow crystalline solid with a yield of 1.53 g (80%). m.p. 81-83^{0}C. ^{1}H NMR $CDCl_3$: δ 4.06 (s, 2H, -CH_2), 4.69 (s, 2H, -CH_2), 7.16 (d, 2H, ArH), 7.31 (d, 2H, ArH). ^{13}C NMR $CDCl_3$: δ 38.0, 51.1, 115.9, 128.9, 139.8, 154.1, 166.9, 169.3. IR (KBr pellet, cm^{-1}): n 1020 (C-F), 1233 (-C-N), 1464 (-CH_2), 1555 (Aromatic –C=C), 1637, 1739 (ring –C=O). Anal. Calcd for $C_{10}H_8FNO_2S$: C, 53.32, H, 3.58, N, 6.22%. Found: C, 53.22, H, 3.46, N, 6.11%.

Antibacterial activity

The synthesized compounds 4(a-i) were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25922), *Pseudomonas aeruginosa* (ATTC-27853) and *Klebsiella pneumoniae* bacterial strains by the disc diffusion method [18]. The discs measuring 6.25 mm in diameter were punched from Whatman no. 1 filter paper. The discs were dispensed to each screw capped bottles and sterilized by dry heat at 140^{0}C for an hour. The test compounds were prepared with different concentrations such as <10 mg/mL and >10 mg/mL in N, N-dimethyl formamide. One milliliter containing 100 times the amount of chemical in each disc was added to each bottle, which contains 100 discs. The discs of each concentration were placed in triplicates in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37^{0}C for 24 h. Ciprofloxacin was used as standard drug at a concentration of 10 mg/mL. Solvent and growth controls were kept separately and the zone of inhibition was noted. The results of screening studies are given in (**Table 1**).

Table 1. Antibacterial activity data of compounds 4(a-i).

Compound	S. aureus	E. coli	P. aeruginosa	K. pneumoniae
4a	6	8	12	9
4b	4	3	2	4
4c	8	7	6	6
4d	15	19	20	16
4e	4	5	4	5
4f	13	15	18	14
4g	2	--	--	3
4h	7	5	6	5
4i	17	18	21	15
Ciprofloxacin	19	20	25	18

Inhibitory zone (diameter) mm of synthesized compounds against tested bacterial strains by disk diffusion method.

Antifungal activity

All the synthesized compounds 4 (a-i) were screened for their antifungal activity against *Candida albicans* (NICM No. 300), *Aspergillus fumigatus* (NICM No. 902), *Aspergillus flavus* (NICM No. 524) and *Penicillium marneffei* in DMF by agar plate disc diffusion method [18]. Sabouraud agar medium was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make suspension of the spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Agar medium of 20 mL was poured into each Petri dish. Excess suspension was decanted and the plates were dried by placing in an incubator at 37^{0}C for 1 h. Using an agar punch, wells were made on the seeded agar plates and <10 mg/mL and >10 mg/mL of the test compounds in N,N-dimethyl formamide were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMF. The Petri dishes were prepared in triplicates and maintained at 37^{0}C for 3 to 4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with Ciclopir oxolamine in DMF as standard. Results of screening studies are given in (**Table 2**).

Table 2. Antifungal activity data of compounds 4(a-i).

Compound	A. fumigatus	A. flavus	P. Marneffei	C. albicans
4a	10	13	13	11
4b	3	4	2	6
4c	10	12	11	10
4d	18	15	17	19
4e	10	13	12	11
4f	17	15	17	15
4g	4	3	3	3
4h	10	12	11	10
4i	19	16	17	18
Ciclopir oxolamine	22	18	20	20

Inhibitory zone (diameter) mm of synthesized compounds against tested fungal strains by disk diffusion method.

Results and discussion

The synthetic pathway starts with the synthesis of thiazolidine-2, 4-dione 2, an important bioactive intermediate in the synthesis. The reaction is completed with microwave irradiation at 140° C for 10 min with 90% yield. In contrast, conventional method needs 12-15 h heating affording about 80% yield. Microwave assisted condensation reaction of thiazolidine-2,4-dione with different alkyl halides and acyl halides afforded *N*-substituted thiazolidine-2,4-dione derivatives 4 (a-i) at 200 Watt in 10 min. Yields varied from 84% to 90%. The schematic diagram of the reaction pathway is depicted in **Scheme 1**.

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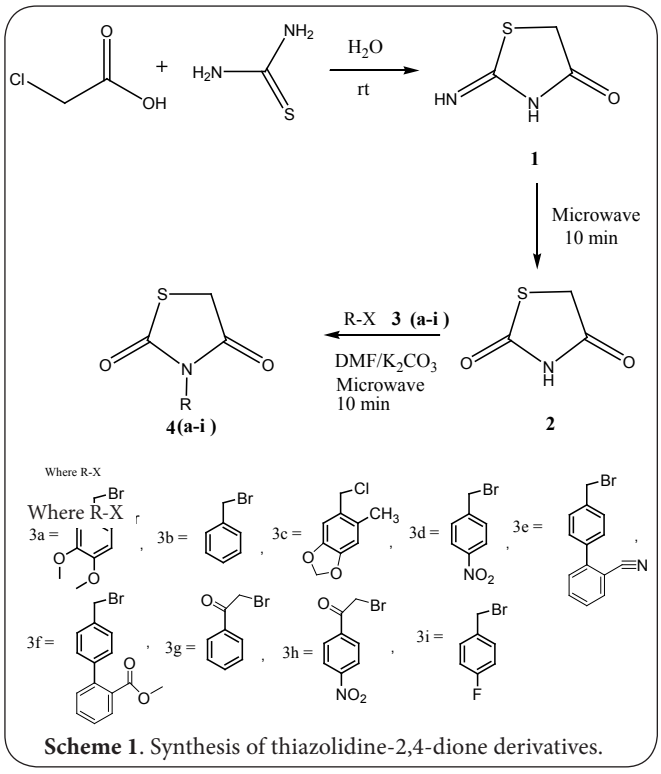

Scheme 1. Synthesis of thiazolidine-2,4-dione derivatives.

The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analyses. The infra red spectra of condensed products showed the disappearance of the peak at 3121 cm^{-1} and this was due to –NH group of thiazolidine-2,4-dione. ^{1}H NMR spectrum of this key intermediate showed a broad singlet at δ 9.1 due to -NH group. Disappearance of this signal in the condensed products confirms their formation. All other substituents were observed in the expected regions. The investigation of the antibacterial and antifungal screening studies revealed that all the tested compounds 4a-i showed moderate to good inhibition in DMF. Compounds 4i with para-fluorobenzyl group and 4d with para-nitrobenzyl group showed comparatively better activity against all the bacterial strains. This better activity can be attributed to the presence of fluoro group and nitro group respectively at para positions of benzene ring. Compound 4f showed moderate activity, due to the presence of methyl carboxylate group on biphenyl ring. Compounds 4a, 4b, 4c, 4e, 4g, and 4h showed weak antibacterial activity. Compounds 4d, 4i and 4f showed good inhibition against all the tested fungal strains. Compounds 4a, 4c, 4e, 4h showed moderate activity while 4b and 4g showed weak antifungal activity.

Conclusions

In conclusion, thiazolidine-2,4-dione and some new derivatives were synthesized and characterized based on their physical and spectral data. Compounds were isolated in good yields and they did not require chromatographic separation owing to microwave irradiation method. Antimicrobial activities of the novel series have been evaluated by disc diffusion method. Compounds 4i and 4d exhibited potent antimicrobial activities. Further research to improve the potency of this series is under progress in our laboratories.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	SLG	NB	NSS	HS
Research concept and design	✓	--	--	--
Collection and/or assembly of data	✓	--	--	--
Data analysis and interpretation	✓	--	--	--
Writing the article	✓	--	--	--
Critical revision of the article	✓	--	--	--
Final approval of article	✓	--	--	--
Statistical analysis	✓	--	--	--

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