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Research Article

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Synthesis and antioxidant activity of some novel derivatives of bis-2-azetidinones and bis-4-thiazolidinones

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Abstract: In present study, several bis- 2-azetidinones **2a-g** and bis-4-thiazolidinones **3a-g** have been synthesized from ethylenediaminebis-Schiff bases using conventional as well as microwave techniques. The newly synthesized compounds were established on the basis of spectroscopic techniques. Further, all compounds were screened for antioxidant activity; most of the titled compounds show potent activity.

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Introduction

Literature survey reveals that most of the compounds having thiazolidiones and azetidinones nuclei possess pharmacological activity [1, 2]. Azetidinones which are part of antibiotic structures are known to exhibit interesting biological activities. A large number of 3-chloro monocyclic β-lactams possesses powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulsant and antitubercular activities [3-5]. They also function as enzyme inhibitors and are effective on the central nervous system [6-8]. 4-Thiazolidinones and its derivatives are known to possess a verity of physiological viz. analgesic local [9] and spiral [10] antimicrobial [11], hypnotics [12], antibacterial [13], antifungal [14], antitubercular [15], anticancer and anti-HIV [16].

The classical synthesis of these compounds involves cycloaddition of monochloroacetyl chloride with imine (Schiff base) resulting in the formation of 2-azetidinone (β-lactam) [17]. Conventional synthesis of 4-thiazolidinones involves the cyclocondensation between the Schiff base and mercaptoacetic acid [18, 19]. As part of our interest towards the development of novel heterocycles [20-24], herein we wish to report the synthesis of bis-2-azetidinones 2a-g and bis-4-thiazolidinones 3a-g by the reaction of bis-imines 1a-g with chloroacetyl chloride and thioglycolic acid, respectively, using conventional as well as microwave technique (Scheme 1).

Materials and Methods

Chemicals and Apparatus

Melting points were determined in an open capillary tube and are uncorrected. FT-IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. 1H NMR spectra were recorded on a Gemini 300-MHz instrument in DMSO as solvent and TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. Synthos-3000, Anton Paar reaction system was used for microwave synthesis.

Synthesis of bis-Schiff bases (1a-g)

Compounds **1a-g** were synthesized according to given method in literature [31]. 1,2-ethylenediamine (0.001 mole) and aldehyde (0.002 mole) were dissolved in ethanol (15 mL), acetic acid (0.2 mL) was added, and the reaction mixture was refluxed for 2-15 min. Reaction was monitored on TLC. Half of the solvent was evaporated and the rest was cooled. The separated solid was filtered, washed with water, and crystallized from ethanol.

General procedure for preparation of bis-2-azetidinones (2a-g); conventional technique

Synthesis of 1,1-ethane-1,2-diylbis(3-chloro-4(3-ethoxy-4-hydroxy-5-iodophenyl)azetidin-2-one (**2c**)

A solution of bis (3-ethoxy-4-hydroxy-5-iodophenyl)benzylidene-1,2-ethylenediamine (0.001 mole, 0.463 mg) in dry dioxane (15 mL) was added to well stirred mixture of chloroacetyl chloride (0.004 mole) and triethyl amine (0.006 mole) in dry 1,4-dioxane at 0^0C. The reaction mixture was stirred for 6 hrs. Excess of solvent was distilled and the resultant solid was poured into ice–cold water. The separated solid was filtered and recrystallized from alcohol to give 2c.

Microwave technique

Synthesis of 1,1-ethane-1,2-diylbis(3-chloro-4(3-ethoxy-4-hydroxy-5-iodophenyl)azetidin-2-one. (2c)

A mixture of bis(3-ethoxy-4-hydroxy-5-iodophenyl)benzylidene-1,2-ethylenediamine (0.001 mole, 0.463 mg) in dry dioxane (15 mL) was taken in conical flask, and chloroacetyl chloride (0.004 mole) and triethyl amine (0.006 mole) were added slowly at 0-5 ^{0}C. Then the reaction mixture was transferred to microwave reaction vessel equipped with a magnetic stirrer (Synthos-3000). The vessel was sealed and the reaction mixture was irraditated by 50 W intermittently at 30 sec. interval for 5 min. The solid so formed was recrystallized from ethyl alcohol to give **2c**. Some of the physical data of the synthesized compounds **2a-g** are given in Table 1.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-ethoxy-4-hydroxyphenyl)azetidin-2-one) (2a)

FT-IR (KBr cm^{-1}): 3480 (Ar-OH stretching), 1670 (C=O stretching), 1470, 1450 (Aromatic C=C stretching), 1380 (C-N stretching). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.35 (t, 6H, -2CH_3), 2.80 (s, 2H, -2CH), 3.68 (s, 4H, -2NCH_2), 4.15 (q, 4H, -2OCH_2), 5.06 (s,2H,-2CH-Cl), 6.32-7.51 (m, 6H, -2ArH), 13.2(s,2H,-2Ar-OH). MS (m/z): 509(M+). Anal. calcd. for $C_{24}H_{26}Cl_2N_2O_6$: C,56.58; H, 5.10. Found: C, 55.28; H, 5.35.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-ethoxy-4-hydroxy-5-bromophenyl)azetidin-2-one) (2b)

FT-IR (KBr cm^{-1}): 3435 (Ar-OH stretching), 1685 (C=O stretching), 1455, 1440 (Aromatic C=C stretching), 1380, 1385 (C-N stretching). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.38 (t, 6H, -2CH_3), 2.85 (s, 2H, -2CH), 3.70 (s, 4H, -2NCH_2), 4.01 (q, 4H, -2OCH_2), 5.12 (s,2H,-2CH-Cl), 6.53-7.80 (m, 4H, -2ArH), 13.01(s,2H,-2Ar-OH). MS (m/z): 667 (M+). Anal. calcd. for $C_{24}H_{24}$ Br_2Cl_2 N_2O_6: C,43.76; H, 3.90. Found: C,43.28; H, 3.35.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-ethoxy-4-hydroxy-5-iodophenyl)azetidin-2-one) (2c)

FT-IR (KBr cm^{-1}): 3410 (Ar-OH stretching), 1690 (C=O stretching), 1440, 1425 (Aromatic C=C stretching), 1370 (C-N stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.35 (t, 6H, -2CH_3), 2.83 (s, 2H, -2CH), 3.65 (s, 4H, -2NCH_2), 4.15 (q, 4H, -2OCH_2), 5.16 (s,2H,-2CH-Cl), 6.65-7.85 (m, 4H, -2ArH), 13.10 (s, 2H,-2Ar-OH). MS (m/z): 761 (M+). Anal. calcd. for $C_{24}H_{24}Cl_2I_2N_2O_6$: C,37.56; H, 3.15. Found: C,37.28; H, 3.35.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-methox-4-hydroxyphenyl)azetidin-2-one) (2d)

FT-IR (KBr cm^{-1}): 3425 (Ar-OH stretching), 1678 (C=O stretching), 1460, 1444 (Aromatic C=C stretching), 1378 (C-N stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.82 (s, 2H, -2CH), 3.40 (s, 4H, -2NCH_2), 3.75 (s, 6H, -2OCH_3), 5.01 (s,2H,-2CH-Cl), 6.25-7.30 (m, 6H, -2ArH), 13.60 (s,2H,-2Ar-OH). MS (m/z): 483 (M+). Anal. calcd. for $C_{22}H_{24}Cl_2N_2O_6$: C,54.56; H, 4.96 Found: C,54.80; H, 4.30.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-methoxy-4-hydroxy-5-bromophenyl)azetidin-2-one) (2e)

FT-IR (KBr cm^{-1}): 3445 (Ar-OH stretching), 1682 (C=O stretching), 1465, 1450 (Aromatic C=C stretching), 1380 (C-N stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.83 (s, 2H, -2CH), 3.43 (s, 4H, -2NCH_2), 3.78 (s, 6H, -2OCH_3), 5.12 (s, 2H,-2CH-Cl), 6.30-7.35 (m, 4H, -2ArH), 13.40 (s, 2H,-2Ar-OH). MS (m/z): 613 (M+). Anal. calcd. for $C_{22}H_{22}Br_2Cl_2\ N_2O_6$: C,43.06; H, 3.58. Found: C, 43.80; H, 3.30.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-methoxy-4-hydroxy-5-chlorophenyl)azetidin-2-one) (2f)

FT-IR (KBr cm^{-1}): 3480(Ar-OH stretching), 1688 (C=O stretching), 1475, 1455 (Aromatic C=C stretching), 1385 (C-N stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.86 (s, 2H, -2CH), 3.47 (s, 4H, -2NCH_2), 3.80 (s, 6H, -2OCH_3), 5.20 (s,2H,-2CH-Cl), 6.42-7.40 (m, 4H, -2ArH), 13.32 (s,2H,-2Ar-OH). MS (m/z): 556 (M+). Anal. calcd. for $C_{22}H_{22}Cl_4N_2O_6$: C,47.48; H, 3.95. Found: C, 47.76; H, 4.00.

1,1-Ethane-1,2-diylbis(3-chloro-4(3-methoxy-4-hydroxy-5-iodophenyl)azetidin-2-one) (2g)

FT-IR (KBr cm^{-1}): 3428 (Ar-OH stretching), 1681 (C=O stretching), 1460, 1445 (Aromatic C=C stretching), 1382 (C-N stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.85 (s, 2H, -2CH), 3.42 (s, 4H, -2NCH_2), 3.69 (s, 6H, -2OCH_3), 5.15 (s,2H,-2CH-Cl), 6.35-7.25 (m, 4H, -2ArH), 13.10 (s,2H,-2Ar-OH). MS (m/z): 640 (M+). Anal. calcd. for $C_{22}H_{22}Cl_2I_2N_2O_6$: C,41.25; H, 3.43. Found: C,41.80; H, 3.56.

General procedure for preparation of bis-4-thiazolidinone

Conventional synthesis of 3,3-ethane-1,2-diylbis(2-(3-ethoxy-4-hydroxy-5-iodophenyl)-1,3-thiazolidin-4-one) (3c)

A mixture of bis(3-ethoxy-4-hydroxy-5-iodophenyl)benzylidene-1,2-ethylenediamine (0.001 mole, 0.462 mg) in 1,4-dioxane (15 mL) containing anhydrous $ZnCl_2$ (0.02 g) and thioglycolic acid (0.002 mole) was refluxed for 8 hrs. The reaction mixture was cooled and poured into ice cold water. The separated solid was filtered and recrystallized from 1,4-dioxane to give **3c**.

Microwave technique

Synthesis of 3,3-ethane-1,2-diylbis(2-(3-ethoxy-4-hydroxy-5-iodophenyl)-1,3-thiazolidin-4-one).(3c)

A homogeneous mixture of bis(3-ethoxy-4-hydroxy-5-iodophenyl)benzylidene-1,2-ethylenediamine (0.001 mole, 0.462 mg) in 1,4-dioxane (15 mL) containing anhydrous $ZnCl_2$ (0.02 g) and thioglycolic acid (0.002 mole) was introduced to a microwave reaction vessel equipped with a magnetic stirrer (Synthos-3000). The vessel was sealed and the reaction was irradiated by 50 W intermittently at 30 sec. interval for 5 min. The solid formed was filtered and recrystallized from ethyl alcohol to give **3c**. Some of the physical data of synthesized compounds **3a-g** are given in Table 2.

3,3-Ethane-1,2-diylbis(2-(3-ethoxy-4-hydroxyphenyl)-1,3-thiazolidin-4-one(3a)

FT-IR (KBr cm^{-1}): 3525 (Ar-OH stretching), 1792 (C=O stretching), 1570, 1530,1440 (Aromatic C=C stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.30 (t, 6H, -2CH_3), 3.29 (s, 2H, -2CH), 4.19 (q, 4H, -2OCH_3), 5.10 (s,4H,-2CH_2-S), 7.20-7.95 (m, 6H, -2ArH), 13.01(s, 2H, -2Ar-OH). MS (m/z): 504 (M^+). Anal. calcd. for $C_{24}H_{28}N_2O_6S_2$: C,57.24; H, 5.50. Found: C,57.80; H, 5.56.

3,3-Ethane-1,2-diylbis(2-(3-ethoxy-4-hydroxy-5-bromophenyl)-1,3-thiazolidin-4-one(3b)

FT-IR (KBr cm^{-1}): 3535 (Ar-OH stretching), 1795 (C=O stretching), 1575, 1540,1450 (Aromatic C=C stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.36 (t, 6H, -2CH_3), 3.32 (s, 2H, -2CH), 4.21 (q, 4H, -2OCH_3), 5.16 (s,4H,-2CH_2-S), 7.30-7.85 (m, 4H, -2ArH), 13.0 (s,2H,-2Ar-OH). MS (m/z): 662 (M^+). Anal. calcd. for $C_{24}H_{26}Br_2N_2O_6S_2$: C,43.50; H, 3.92. Found: C,43.70; H, 3.96.

3,3-Ethane-1,2-diylbis(2-(3-ethoxy-4-hydroxy-5-iodophenyl)-1,3-thiazolidin-4-one (3c)

FT-IR (KBr cm^{-1}): 3530(Ar-OH stretching), 1790 (C=O stretching), 1555, 1530,1450 (Aromatic C=C stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.28 (t, 6H, -2CH_3), 3.29 (s, 2H, -2CH), 4.18 (q, 4H, -2OCH_3), 4.96 (s,4H,-2CH_2-S), 7.35-7.75 (m, 4H, -2ArH), 13.05 (s, 2H, -2Ar-OH). MS (m/z): 756 (M^+). Anal. calcd. for $C_{24}H_{26}I_2N_2O_6S_2$: C, 38.09; H, 3.43. Found: C,38.26; H, 3.56.

3,3-Ethane-1,2-diylbis(2-(3-methoxy-4-hydroxyphenyl)-1,3-thiazolidin-4-one(3d)

FT-IR (KBr cm^{-1}): 3525 (Ar-OH stretching), 1788 (C=O stretching), 1553, 1540,1435 (Aromatic C=C stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.30 (s, 2H, -2CH), 3.50 (s, 4H, -2NCH_2), 3.70 (s, 6H, -2OCH_3), 4.86 (s,4H,-2CH_2-S), 7.38-7.80 (m, 6H, -2ArH), 12.05 (s,2H,-2Ar-OH). MS (m/z): 476 (M^+). Anal. calcd. for $C_{22}H_{24}N_2O_6S_2$: C,55.46; H, 5.04. Found: C,54.50; H, 5.25.

3,3-Ethane-1,2-diylbis(2-(3-methoxy-4-hydroxy-5-bromophenyl)-1,3-thiazolidin-4-one(3e)

FT-IR (KBr cm^{-1}): 3540 (Ar-OH stretching), 1793 (C=O stretching), 1558, 1545,1440 (Aromatic C=C stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.32 (s, 2H, -2CH), 3.53 (s, 4H, -2NCH_2), 3.73 (s, 6H, -2OCH_3), 4.88 (s,4H,-2CH_2-S), 7.40-7.85 (m, 4H, -2ArH), 12.14 (s, 2H, -2Ar-OH). MS (m/z): 634 (M^+). Anal. calcd. for $C_{22}H_{22}Br_2N_2O_6S_2$: C, 41.64; H, 3.47. Found: C,41.30; H, 3.80.

3,3-Ethane-1,2-diylbis(2-(3-methoxy-4-hydroxy-5-chlorophenyl)-1,3-thiazolidin-4-one(3f)

FT-IR (KBr cm^{-1}): 3550 (Ar-OH stretching), 1794 (C=O stretching), 1568, 1555, 1450 (Aromatic C=C stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.35 (s, 2H, -2CH), 3.56 (s, 4H, -2NCH_2), 3.78 (s, 6H, -2OCH_3), 4.89 (s,4H,-2CH_2-S), 7.43-7.85 (m, 4H, -2ArH), 13.14 (s, 2H, -2Ar-OH). MS (m/z): 546 (M^+). Anal. calcd. for $C_{22}H_{22}Cl_2N_2O_6S_2$: C, 48.35; H, 4.09. Found: C, 48.20; H, 4.20.

3,3-Ethane-1,2-diylbis(2-(3-methoxy-4-hydroxy-5-iodophenyl)-1,3-thiazolidin-4-one(3g)

FT-IR (KBr cm^{-1}): 3520 (Ar-OH stretching), 1790 (C=O stretching), 1550, 1530,1452 (Aromatic C=C stretching). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.27 (s, 2H, -2CH), 3.41 (s, 4H, -2NCH_2), 3.69(s, 6H, -2OCH_3), 4.81 (s,4H,-2CH_2-S), 7.31-7.75 (m, 4H, -2ArH), 13.01 (s, 2H, -2Ar-OH). MS (m/z): 728 (M^+). Anal. calcd. for $C_{22}H_{22}I_2N_2O_6S_2$: C,36.26; H, 3.02. Found: C, 36.40; H, 4.30.

Antioxidative activity

The following antioxidative methods were used to evaluate the antioxidative properties of our test compounds.

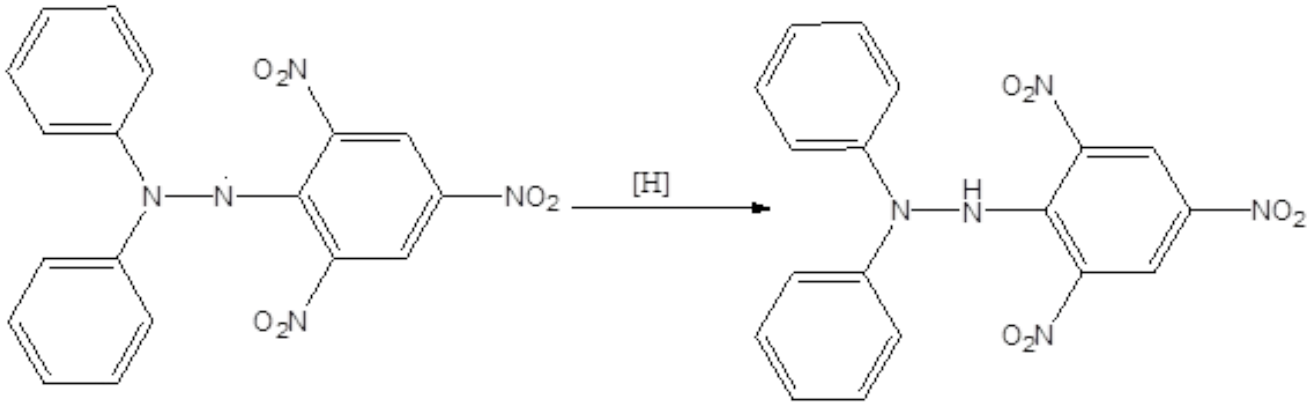
DPPH• Scavenging Activity

DPPH is a stable free radical that can accept an electron or hydrogen radical to become a stable diamagnetic molecule. Due to its odd electron, the methanolic solution of DPPH shows a strong absorption band at 517 nm. DPPH radical reacts with various electron donating molecules (reducing agents or antioxidants). When electrons become paired off, the result is that DPPH solution is bleached. This results in the formation of the colorless 2,2'-diphenyl-1-picryl hydrazine. Reduction of the DPPH radicals can be estimated quantitatively by measuring the decrease in absorbance at 517 nm.

Procedure: Equal volumes of 100 µM 2,2'-diphenyl-1-picrylhydrazyl (DPPH) in methanol was added to different concentrations of test compounds (0 – 200 µM/mL) in methanol, mixed well and kept in dark for 20 min. The absorbance at 517 nm was measured using the Shimadzu UV-1650 spectrophotometer. Plotting the percentage DPPH• scavenging against concentration gave the standard curve and the percentage scavenging was calculated from the following equation:

$$\%\text{scavenging} = \frac{\text{Absorbance of blank} - \text{Absorbance of test}}{\text{Absorbance of blank}} \times 100$$

IC50 was obtained from a plot between concentration of test compounds and % scavenging. Ascorbic acid was used as standard for comparison.



Structural changes occur with DPPH during oxidation

Nitric Oxide Scavenging Activity

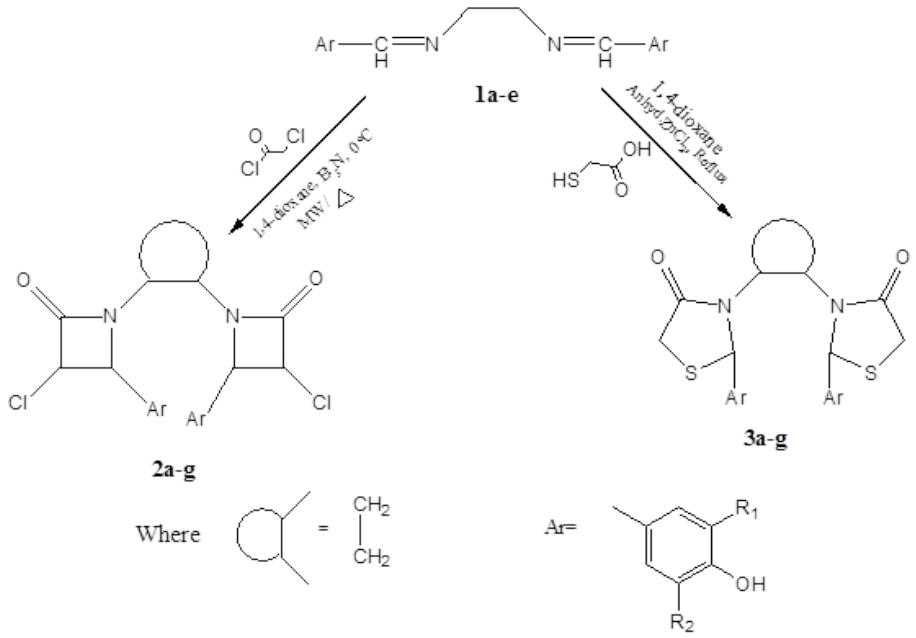
Nitric oxide (NO) will be generated by sodium nitroprusside in solution. In the presence of an antioxidant or nitric oxide scavenger, the amount of NO generated will be less. The excess NO will be estimated by Griess reagent, which is the mixture of sulfanilic acid and naphthylethylenediamine dihydrochloride. The nitric oxide will give pink colored complex estimated at 540 nm.

Procedure: To a reaction mixture (6 mL) containing sodium nitroprusside (10 mM, 4 mL), phosphate buffer saline (PBS, 1.0 mL) and 1.0 mL of different concentration of test compounds/standard were incubated at 25ºC for 150 min. After incubation, 0.5 mL of the reaction mixture containing nitrate was removed and 1.0 mL of sulfanilic acid was added, mixed well and allowed to stand for 5 min for completion of diazotization. Then 1.0 mL of naphthylethylenediamine dihydrochloride was added, mixed and allowed to stand for 30 min in dark at room temperature.

The absorbance of these solutions was measured at 540 nm against corresponding blank solution without sodium nitroprusside [29-30]. The % scavenging and IC50 values were determined as explained in DPPH assay.

Results and discussion

In view of the importance of this class of heterocycles and in continuation of our earlier investigations, we have reported the synthesis of 4-thiazolidinones from imines and some of the thiazolidinones were found to have antibacterial action [25]. Therefore, in the present paper, we synthesized a new class of bis- 2-azetidinones and bis-4-thiazolidinones by cyclocondensation reaction of imines 1a-g (Scheme 1). The halo-substituted hydroxybenzaldehydes required for the preparation of imines were prepared by iodination of substituted hydroxybenzaldehydes using molecular iodine and iodic acid by refluxing technique [26]. The 1a-g on cyclocondensation with chloroacetyl chloride afford bis-2-azetidinones 2a-g and with thioglycolic acid afford bis-4-thiazolidinones 3a-g using both conventional as well as MWI techniques. MWI technique were used over conventional technique due to the application of microwave (MW) irradiation as a non-conventional energy source for activation of reactions has now become a very popular and useful technology in organic chemistry [27]. Many researchers have described accelerated organic reactions towards proving the synthetic utility of MW irradiation in routine organic synthesis [28]. Thus, MW techniques has many advantages including easy work-up procedure, short reaction time, and does not need any effort for isolation of products giving high percentage yields. The structures of newly synthesized compounds 2a-g & 3a-g respectively, have been confirmed by elemental analysis, FT-IR, NMR and MS spectral studies. In 1H NMR spectra of bis-2-azetidinones obtained at δ value 2.85 and δ near 5.0 is due to proton of CH-N and CH-Cl respectively. The 1H NMR spectra of bis-4-thiazolidinones show characteristics δ value at 4.90 due to two protons of –CH2S. The δ value at 3.32 is due to –CH of five-membered thiazolidinone ring.



Scheme 1: Synthesis of some novel derivatives of bis-2-azetidinones and bis-4-thiazolidinones

The DPPH is a stable radical that can accept hydrogen radical to become a stable diamagnetic molecule. Due to its odd electron, alcoholic solution of DPPH shows a strong absorption at 517 nm. Therefore, DPPH readily reacts with reducing agent to yield colorless 2, 2'-diphenyl -1-picrylhydrazine. Reduction of the DPPH radicals can be determined quantitatively by measuring the decrease in absorbance at 517 nm.

Nitric oxide is generated by sodium nitroprusside in solution. In the presence of an antioxidant, the amount of NO generated will be less. The excess of NO estimated by Griess reagent, which is composed of the mixture of H_2SO_4 and naphthylethylene diamine.

The results of antioxidant activity expressed as IC50 value with two different antioxidant agents are shown in Table 3. The compounds 2c, 2f, 3c and 3f were tested using DPPH scavenging method and they showed IC50 value at 70.20, 70.28, 70.30, and 70.13 μM, when compared with that of the standard ascorbic acid at 69.08 μM, respectively. However the compound 2d and 2e did not show significant activity. Further, the antioxidant studies carried out using NO scavenging method, the only compounds 2c, 2g, 3c, and 3g showed IC50 value at 92.10, 91.25, 92.00 and 92.20 μM in comparison with standard, respectively. The compounds 2e and 3e did not show antioxidant activity.

Table 1: Physical and analytical data for bis-2-azetidinones.

Entry	R_1	R_2	mp, ^{0}C	% yield, CM	% yield, MW
2a	OEt	H	158	68	80
2b	OEt	Br	210	70	85
2c	OEt	I	220	75	90
2d	OMe	H	150	80	95
2e	OMe	Br	175	68	85
2f	OMe	Cl	180	70	84
2g	OMe	I	200	72	85

NB: CM: Conventional method, MW: Microwave method.

Table 2: Physical and analytical data for bis-4–thiazolidinones.

Entry	R_1	R_2	mp, ^{0}C	% yield, CM	% yield, MW
3a	OEt	H	178	70	85
3b	OEt	Br	190	75	85
3c	OEt	I	160	75	90
3d	OMe	H	155	80	95
3e	OMe	Br	215	75	85
3f	OMe	Cl	185	70	84
3g	OMe	I	170	74	85

Table 3: Antioxidant activity of bis- 2-azetidinones and bis-4-thiazolidinones.

Entry	DPPH scavenging (μM)	NO scavenging (μM)
2a	78.07	97.89
2b	85.27	105.64
2c	70.20	92.10
2d	NSA	146.97
2e	170.12	165.24
2f	70.28	96.28
2g	126.41	91.25
3a	83.59	116.93
3b	73.09	94.68
3c	70.30	92.00
3d	78.53	99.14
3e	NSA	107.47
3f	70.13	96.10
3g	125.15	92.20
Standard	69.08*	91.05*

Conclusion

In conclusion, the salient feature of our approach is coupling microwave with keeping modernization over classical procedure for the synthesis of bis-2-azetidinones and bis-4-thiazolidinones. The microwave technique is found to be efficient and cheap for the synthesis of mentioned compounds. In continuation of previously published results [32] and as a part of our research work, focus has been given on the development of new bis-2-azetidinones and bis-4-tiazolidinones as a bioactive agents. Synthesis and preliminary antioxidant screening of new bis-2-azetidinones and bis-4-thiazolidinones have been demonstrated. The presence of halogen atom in the compounds provides a positive influence on antioxidant activity. Owing to encouraging results, it was found that the synthesized compounds have broader value of activity than standard used for screening of antioxidant activity. The electronic effect also played a role in activity, as can be screen for the compounds having electron donor character such as –OEt, -OMe and –OH. Thus in future, this class of compounds may be used as templates for generating better lead molecules as a antioxidant agents.

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