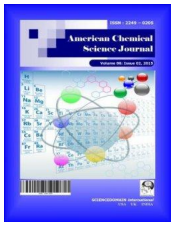

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Synthesis of New 4-(dimethylamino)benzhydrazide Derivatives and Their Cyclization to 1,3-benzothiazin-4-one Moiety

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Author's contribution

Author ŁP design the study, performed the synthesis of new 2,3-disubstituted derivatives of 1,3-benzothiazin-4-one, analyzed the spectral data of obtained compounds and wrote the manuscript. Author read and approved the final manuscript.

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Short Research Article

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ABSTRACT

The reaction of hydrazides of carboxylic acids with aldehydes is an efficient synthetic method to produce *N*-substituted hydrazone derivatives. The resulting hydrazone compounds are considered as convenient intermediates and can be used to obtain new interesting heterocyclic systems e.g. 1,3-thiazolidin-4-one or 1,3-benzothiazin-4-one derivatives. In the present work such pathway was used for the synthesis of new 1,3-benzothiazin-4-one derivatives (16-30). New compounds were obtained by the cyclization reaction of *N*-substituted 4-(dimethylamino)benzhydrazides (1-15) with thiosalicylic acid. The spectral (IR, ^{1}H NMR, ^{13}C NMR) and elemental analysis confirmed the structure of synthesized compounds.

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Keywords: Benzhydrazide derivatives; 1,3-benzothiazine derivatives; condensation reaction; cyclization reaction.

1. INTRODUCTION

The 1,3-benzothiazin-4-ones derivatives, in recent years, have gained substantial interest in the scientific community not only due to their meaningful biological activity, but also as reactive intermediates to lots of new synthetic transformations [1,2]. Many 1,3-benzothiazin-4-one derivatives exhibit a broad spectrum of biological activities, so that the purposeful of their synthesis and modification of their structure attracts great interest in pharmacology and other related fields [1,2].

Some compounds having the 1,3-benzothiazin-4-one structure have been reported to exhibit biological activities, like antiproliferative [2,3], antibacterial [4-8], antifungal [9,10], antimalarial [11], anti-inflammatory [12] and antiviral activity, mainly against HIV virus [13] and several efficient routes to synthesis of such compounds have been published [2,12].

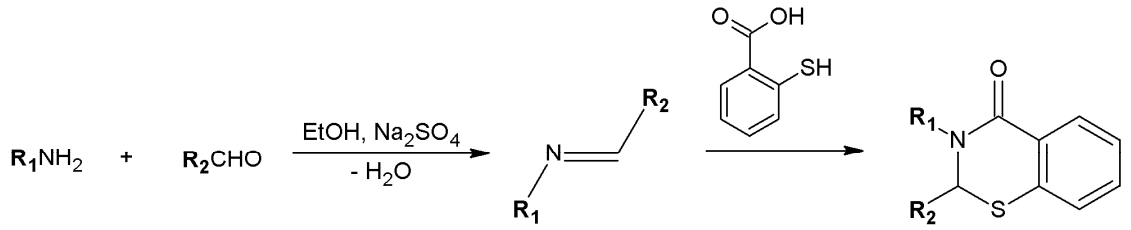
Generally, methods for preparing these compounds rely on the simultaneous reaction of three components or on a two-step synthesis (Scheme 1). During the first stage of synthesis the following starting materials are used: compound with primary amine group and an aldehyde. Next, in the second step the resulting intermediate undergoes cyclization reaction with thiosalicylic acid. The anhydrous 1,4-dioxane or toluene [2,12] with the addition of anhydrous sodium sulfate [2] are used as reaction medium.

Basing on the above facts, in this paper I wish to report the synthesis and spectral analysis of a new class of 1,3-benzothiazin-4-ones obtained by cyclization reaction of *N*-substituted 4-(dimethylamino)benzhydrazides.

2. EXPERIMENTAL DETAILS

2.1 General

All reagents were purchased from Sigma-Aldrich (Munich, Germany) and Merck Co. (Darmstadt, Germany) and used without further purification. Melting points were determined in Fisher-Johns blocks (Fisher Scientific, Germany) and presented without any corrections. The IR spectra (v, cm^{-1}) were recorded in KBr tablets using a Specord IR-75 spectrophotometer (VEB Carl Zeiss, Jena, Germany). The ^{1}H NMR spectra were recorded on a Bruker Avance DPX 250 MHz apparatus (Bruker BioSpin GmbH, Germany) in DMSO-d_6 with TMS as internal standard. The ^{13}C NMR spectra were recorded on a Bruker Avance DPX 250 MHz apparatus. Chemical shifts are given in ppm (δ-scale). The MS spectra were recorded on a Thermo-Finnigan Trace DSQ GC MS apparatus (Waltham, Massachusetts, USA).The purity of obtained compounds was checked by TLC on aluminium oxide 60 F254 plates (Merck Co. USA), in a $CHCl_3/C_2H_5OH$ (10:1, v/v) solvent system. The spots were detected by exposure to a UV lamp at 254 nm. Elemental analyses of the obtained compounds was performed for C, H, N on AMZ 851 CHX analyser (PG, Gdańsk, Poland). The maximum percentage differences between calculated and found values for each element were within the error and amounted to ±0.4%.



R_1, R_2 = Alkyl or Aryl

Scheme 1. Classical two step synthesis of 2,3-disubstituted 1,3-benzothiazin-4-one derivatives

2.2 Synthesis of *N*-substituted derivatives of 4-(dimethylamino)benzhydrazide (1-15)

To the solution of 10 mmol of 4-(dimethylamino) benzhydrazide (1.79 g) in ethanol (10 mL) 10 mmol of appropriate aromatic aldehyde and a few drops of glacial acetic acid were added. The solution was heated under reflux for 3 hrs. After the completion of the reaction, the solution was cooled to room temperature and left at room temperature for 24 hrs. The obtained precipitate was filtered off and crystallized from ethanol.

N-[(2-chlorophenyl)methylidene]-4-(dimethylamino)benzhydrazide (1)

CAS Number: 199791-09-8, Yield: 28%, M.p.: 226-228ºC, IR (KBr), ν (cm^{-1}): 3050 (CH aromatic), 3010, 1451 (CH aliphatic), 1703 (C=O), 1618 (C=N), 1598 (NH), 1398 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 3.01 (s, 6H, 2xCH_3), 6.75-6.79 (dd, 2H, ArH, *J* = 10Hz), 7.40-7.47 (m, 2H, ArH), 7.50-7.55 (m, 2H, ArH), 7.82-7.86 (dd, 2H, ArH, *J* = 10Hz), 7.99 (s, 1H, =CH), 11.82 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.4, 121.9, 127.4, 127.5, 128.7, 130.3, 130.9, 131.31, 132.8 (11C_{ar}), 149.9 (=CH), 152.9 (C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{16}ClN_3O$ (301.77) Calculated: C: 63.68%, H: 5.34%, N: 13.92%, Found: C: 63.72%, H: 5.32%, N: 13.96%.

N-[(3-chlorophenyl)methylidene]-4-(dimethylamino)benzhydrazide (2)

CAS Number: 401638-22-0, Yield: 76%, M.p.: 238-244ºC, IR (KBr), ν (cm^{-1}): 3040 (CH aromatic), 3015, 1455 (CH aliphatic), 1708 (C=O), 1614 (C=N), 1595 (N-H), 1403 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 3.00 (s, 6H, 2xCH_3), 6.75-6.78 (dd, 2H, ArH, *J* = 7.5Hz), 7.47-7.53 (m, 2H, ArH), 7.65-7.68 (m, 1H, ArH), 7.74-7.84 (m, 1H, ArH), 7.81-7.84 (dd, 2H, ArH, *J* = 7.5Hz), 8.40 (s, 1H, =CH), 11.70 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.3, 121.9, 125.1, 127.6, 128.0, 130.2, 130.3, 134.1, 135.3 (11C_{ar}), 148.7 (=CH), 152.9 (C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{16}ClN_3O$ (301.77) Calculated: C: 63.68%, H: 5.34%, N: 13.92%, Found: C: 63.74%, H: 5.31%, N: 13.91%.

N-[(4-chlorophenyl)methylidene]-4-(dimethylamino)benzhydrazide (3)

CAS Number: 401638-18-4, Yield: 65%, M.p.: 212-214ºC, IR (KBr), ν (cm^{-1}): 3058 (CH aromatic), 3035, 1447 (CH aliphatic), 1710 (C=O), 1622 (C=N), 1604 (N-H), 1406 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 3.00 (s, 6H, 2xCH_3), 6.70-6.74 (dd, 2H, ArH, *J* = 10Hz), 7.50-7.53 (dd, 2H, ArH, *J* = 7.5Hz), 7.71-7.75 (dd, 2H, ArH, *J* = 10Hz), 7.81-7.84 (dd, 2H, ArH, *J* = 7.5Hz), 8.41 (s, 1H, =CH), 11.63 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.4, 121.9, 129.1, 129.4, 130.3, 134.11, 135.13 (11C_{ar}), 149.3 (=CH), 152.9 (C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{16}ClN_3O$ (301.77): Calculated: C: 63.68%, H: 5.34%, N: 13.92%, Found: C: 63.65%, H: 5.36%, N: 13.95%.

N-[(2-bromophenyl)methylidene]-4-(dimethylamino)benzhydrazide (4)

Yield: 72%, M.p.: 215-218ºC, IR (KBr), ν (cm^{-1}): 3035 (CH aromatic), 3010, 1459 (CH aliphatic), 1715 (C=O), 1615 (C=N), 1605 (N-H), 1395 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.00 (s, 6H, 2xCH_3), 5.75-5.78 (dd, 2H, ArH, *J* = 7.5Hz), 6.31-6.38 (m, 1H, ArH), 6.44-6.50 (m, 1H, ArH), 6.68-6.71 (m, 1H, ArH), 6.84-6.87 (dd, 2H, ArH, *J* = 7.5Hz), 6.98-7.01 (m, 1H, ArH), 7.79 (s, 1H, =CH), 10.85 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41,9 (2xCH_3), 110.4, 121.9, 124.6, 127.1, 127.8, 128.0, 130.3, 132.6, 133.4 (11C_{ar}), 146.1 (=CH), 152.9 (C_{ar}), 164.2 (C=O). Analysis for $C_{16}H_{16}BrN_3O$ (346.22) Calculated: C: 55.51%, H: 4.66%, N: 12.14%, Found: C: 55.47%, H: 4.68%, N: 12.11%.

N-[(3-bromophenyl)methylidene]-4-(dimethylamino)benzhydrazide (5)

CAS Number: 525564-95-8, Yield: 77%, M.p.: 236-238ºC, IR (KBr), ν (cm^{-1}): 3041 (CH aromatic), 3022, 1449 (CH aliphatic), 1709 (C=O), 1610 (C=N), 1601 (N-H), 1401 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.00 (s, 6H, 2xCH_3), 5.75-5.78 (dd, 2H, ArH, *J* = 7.5Hz), 6.39-6.45 (m, 1H, ArH), 6.59-6.63 (m, 1H, ArH), 6.68-6.71 (m, 1H, ArH), 6.81-6.84 (dd, 2H, ArH, *J* = 7.5Hz), 6.89-6.91 (m, 1H, ArH), 7.38 (s, 1H, =CH), 10.70 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.4, 121.9, 123.9, 125.7, 129.7, 129.9, 130.3, 130.6, 137.1 (11C_{ar}), 148.7 (=CH), 152.9 (C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{16}BrN_3O$ (346.22) Calculated: C: 55.51%, H: 4.66%, N: 12.14%, Found: C: 55.47%, H: 4.68%, N: 12.16%.

N-[(4-bromophenyl)methylidene]-4-(dimethylamino)benzhydrazide (6)

CAS Number: 330640-38-5, Yield: 77%, M.p.: 208-210ºC, IR (KBr), ν (cm^{-1}): 3052 (CH

aromatic), 3015, 1454 (CH aliphatic), 1710 (C=O), 1618 (C=N), 1608 (N-H), 1408 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.00 (s, 6H, 2xCH_3), 5.74-5.78 (dd, 2H, ArH, *J* = 10Hz), 6.23-6.26 (dd, 2H, ArH, *J* = 7.5Hz), 6.64-6.68 (dd, 2H, ArH, *J* = 10Hz), 6.81-6.84 (dd, 2H, ArH, *J* = 7.5 Hz), 7.40 (s, 1H, =CH), 10.63 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.4, 121.9. 123.9, 129.3, 130.3, 132.4, 132.5 (11C_{ar}), 149.3 (=CH), 152.6 (C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{16}BrN_3O$ (346.22): Calculated: C: 55.51%, H: 4.66%, N: 12.14%, Found: C: 55.58%, H: 4.68%, N: 12.16%.

N-[(2-fluorometylidene]-4-(dimethylamino)benzhydrazide (7)

CAS Number: 525565-89-3, Yield: 78%, M.p.: 210-212ºC, IR (KBr), ν (cm^{-1}): 3055 (CH aromatic), 3030, 1460 (CH aliphatic), 1715 (C=O), 1590 (C=N), 1602 (N-H), 1401 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.00 (s, 6H, 2xCH_3), 5.75-5.78 (dd, 2H, ArH, *J* = 7.5Hz), 6.22-6.33 (m, 2H, ArH), 6.44-6.52 (m, 1H, ArH), 6.83-6.97 (dd, 2H, ArH, *J* = 7.5Hz), 6.91-6.97 (m, 1H, ArH), 7.67 (s, 1H, =CH), 10.70 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.4, 117.4, 121.9, 124.5, 125.3, 129.4, 130.3, 130.8 (10C_{ar}), 149.3 (=CH), 152.9, 160.4 (2C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{16}FN_3O$ (285.32) Calculated C: 67.35%, H: 5.65%, N: 14.73%, Found: C: 67.38%, H: 5.63%, N: 14.76%.

N-[(3-fluorometylidene]-4-(dimethylamino)benzhydrazide (8)

CAS Number: 525565-82-6, Yield: 84%, M.p.: 252-254ºC, IR (KBr), ν (cm^{-1}): 3068 (CH aromatic), 3024, 1451 (CH aliphatic), 1705 (C=O), 1604 (C=N), 1598 (N-H), 1393 (C-N).^{1}H NMR (DMSO-d_6) δ (ppm) = 2.00 (s, 6H, 2xCH_3), 5.75-5.78 (dd, 2H, ArH, *J* = 7.5Hz), 6.22-6.30 (m, 1H, ArH), 6.46-6.56 (m, 3H, ArH), 6.81-6.84 (dd, 2H, ArH, *J* = 7.5Hz), 7.43 (s, 1H, =CH), 10.67 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.4, 114.2, 116.9, 121.9, 138.6 (10C_{ar}), 148.7 (=CH), 152.9, 162.7 (2C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{16}FN_3O$ (285.32) Calculated: C: 67.35%, H: 5.65%, N: 14.73%, Found: C: 67.41%, H: 5.67%, N: 14.70%.

N-[(4-fluorometylidene]-4-(dimethylamino)benzhydrazide (9)

CAS Number: 525561-74-4, Yield: 72%, M.p.: 210-212ºC, IR (KBr), ν (cm^{-1}): 3045 (CH aromatic), 3022, 1455 (CH aliphatic), 1711 (C=O), 1612 (C=N), 1591 (N-H), 1395 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.00 (s, 6H, 2xCH_3), 5.74-5.78 (dd, 2H, ArH, *J* = 10Hz), 6.26-6.32 (m, 2H, ArH), 6.74-6.79 (m, 2H, ArH), 6.80-6.84 (dd, 2H, ArH, *J* = 10Hz), 7.42 (s, 1H, =CH), 10.57 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.4, 115.5, 121.9, 130.3, 130.4, 130.8 (10C_{ar}), 149.4 (=CH), 152.9, 161.3 (2C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{16}FN_3O$ (285.32) Calculated: C: 67.35%, H: 5.65%, N: 14.73%, Found: C: 67.39%, H: 5.62%, N: 14.76%.

N-[(2-chloro-6-fluorophenyl)methylidene]-4-(dimethylamino)benzhydrazide (10)

CAS Number: 419554-24-8, Yield: 68%, M.p.: 230-233ºC, IR (KBr), ν (cm^{-1}): 3090 (CH aromatic), 3052, 1451 (CH aliphatic), 1703 (C=O), 1639 (C=N), 1612 (N-H), 1405 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.00 (s, 6H, 2xCH_3), 5.74-5.78 (dd, 2H, ArH, *J* = 10Hz), 6.29-6.37 (m, 1H, ArH), 6.43-6.51 (m, 2H, ArH), 6.83-6.87 (dd, 2H, ArH, *J* = 10Hz), 7.66 (s, 1H, =CH), 10.78 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.4, 116.5, 121.9, 125.9, 126.8, 130.3, 131.2, 135.3 (10C_{ar}), 139.9 (=CH), 152.9, 160.1 (2C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{15}ClFN_3O$ (319.76) Calculated: C: 60.10%, H: 4.73%, N: 13.14%, Found: C: 60.14%, H: 4.70%, N: 13.16%.

N-[(3-bromo-4-methoxyphenyl)methylidene]-4-(dimethylamino)benzhydrazide (11)

Yield: 81%, M.p.: 222-224°C, IR (KBr), ν (cm^{-1}): 3085 (CH aromatic), 3066, 1457 (CH aliphatic), 1709 (C=O), 1638 (C=N), 1618 (N-H), 1411 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.00 (s, 6H, 2xCH_3), 2.90 (s, 3H, CH_3), 5.74-5.78 (dd, 2H, ArH, *J* = 10Hz), 6.18-6.21 (m, 1H, ArH), 6.65-6.70 (m, 1H, ArH), 6.79-6.83 (dd, 2H, ArH, *J* = 10Hz), 6.91-6.94 (m, 1H, ArH), 7.34 (s, 1H, =CH), 10.56 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 56.8 (CH_3), 110.4, 114.3, 121.9, 126.9, 129.1, 130.3, 132.3 (10C_{ar}), 148.7 (=CH), 152.9, 157.2 (2C_{ar}), 164.2 (C=O). Analysis for $C_{17}H_{18}BrN_3O_2$ (376.25) Calculated: C: 54.27%, H: 4.82%, N: 11.17%, Found: C: 54.31%, H: 4.80%, N: 11.19%.

N-[(3-bromo-4-hydroxyphenyl)methylidene]-4-(dimethylamino)benzhydrazide (12)

Yield: 74%, M.p.: 252-254ºC, IR (KBr), ν (cm^{-1}): 3590 (O-H), 3038 (CH aromatic), 3011, 1456 (CH aliphatic), 1703 (C=O), 1629 (C=N), 1601 (N-H), 1398 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.99 (s, 6H, 2xCH_3), 5.73-5.77 (d, 2H, ArH, *J* = 10Hz), 6.00-6.03 (m, 1H, ArH), 6.52-6.55 (m, 1H,

ArH), 6.79-6.83 (m, 3H, ArH), 7.29 (s, 1H, =CH), 9.76 (s, 1H, OH), 10.49 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 109.9, 110.4, 116.3, 121.9, 127.2, 128.4, 130.3, 130.4 (10C_{ar}), 148.7 (=CH), 152.9, 153.7 (2C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{16}BrN_3O_2$ (362.22) Calculated: C: 53.05%, H: 4.45%, N: 11.60%, Found: C: 53.09%, H: 4.43%, N: 11.61%.

N-[(5-bromo-2-hydroxyphenyl)methylidene]-4-(dimethylamino)benzhydrazide (13)

CAS Number: 360057-88-1, Yield: 83%, M.p.: 246-248ºC, IR (KBr), ν (cm^{-1}): 3602 (O-H), 3070 CH aromatic), 3026, 1458 (CH aliphatic), 1722 (C=O), 1611 (C=N), 1606 (N-H), 1407 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.00 (s, 6H, 2xCH_3), 5.75-5.78 (dd, 2H, ArH, *J* = 7.5Hz), 5.88-5.92 (m, 1H, ArH), 6.39-6.43 (m, 1H, ArH), 6.74-6.77 (m, 1H, ArH), 6.82-6.85 (dd, 2H, ArH, *J* = 7.5Hz), 7.56 (s, 1H, =CH), 10.54 (s, 1H, OH), 10.94 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.4, 114.6, 118.9, 119.3, 121.9, 130.3, 130.4 (10C_{ar}), 149.6 (=CH), 152.9, 156.3 (2C_{ar}), 164.3 (C=O). Analysis for $C_{16}H_{16}BrN_3O_2$ (362.22) Calculated: C: 53.05%, H: 4.45%, N: 11.60%, Found: C: 53.09%, H: 4.47%, N: 11.64%.

N-[(2-bromo-3-fluorophenyl)methylidene]-4-(dimethylamino)benzhydrazide (14)

Yield: 65%, M.p.: 216-218ºC, IR (KBr), ν (cm^{-1}): 3079 (CH aromatic), 3050, 1448 (CH aliphatic), 1714 (C=O), 1625 (C=N), 1593 (N-H), 1403 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.01 (s, 6H, 2xCH_3), 5.75-5.79 (dd, 2H, ArH, *J* = 10Hz), 6.23-6.31 (m, 1H, ArH), 6.66-6.78 (m, 2H, ArH), 6.83-6.87 (dd, 2H, ArH, *J* = 10Hz), 7.75 (s, 1H, =CH), 10.94 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 110.4, 113.8, 116.2, 121.9, 122.3, 127.8, 130.3, 137.6 (10C_{ar}), 144.9 (=CH), 152.9, 160.8 (2C_{ar}), 164.1 (C=O). Analysis for $C_{16}H_{15}BrFN_3O$ (364.21) Calculated: C: 52.76%, H: 4.15%, N: 11.54%, Found: C: 52.78%, H: 4.11%, N: 11.57%.

N-[(3-chloro-4-methoxyphenyl)methylidene]-4-(dimethylamino)benzhydrazide (15)

Yield: 71%, M.p.: 224-226ºC, IR (KBr), ν (cm^{-1}): 3015 (CH aromatic), 2995, 1455 (CH aliphatic), 1711 (C=O), 1615 (C=N), 1606 (N-H), 1398 (C-N). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.00 (s, 6H, 2xCH_3), 2.91 (s, 3H, CH_3), 5.74-5.77 (d, 2H, ArH, *J* = 7.5Hz), 6.22-6.25 (m, 1H, ArH), 6.63-6.66 (m, 1H, ArH), 6.78-6.83 (m, 3H, ArH), 7.34 (s, 1H, =CH), 10.56 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 56.8 (CH_3), 110.4, 115.5, 121.9, 123.3, 125.5, 127.45, 130.3, 130.7 (10C_{ar}), 148.7 (=CH), 152.9, 156.2 (2C_{ar}), 164.3 (C=O). Analysis for $C_{17}H_{18}ClN_3O_2$ (331.80) Calculated: C: 61.54%, H: 5.47%, N: 12.66%, Found: C: 61.57%, H: 5.49%, N: 12.64%.

2.3 Synthesis of 2,3-disubstituted 1,3-benzothiazin-4-one derivatives (16-30)

To a solution of *N*-substituted derivatives of 4-(dimethylamino)benzhydrazide **1**-**15** (10 mmol) in 15 mL of 1,4-dioxane, thiosalicylic acid (1.54g, 10 mmol) was added. The mixture was stirred under reflux for 6 hrs at 130ºC. After the completion of the reaction, the solution was cooled to room temperature and left at room temperature for 24 hrs. Then the solvent was removed under reduced pressure. After that 15 mL of 10% water solution of sodium bicarbonate was added. The precipitate was filtered off and purified by recrystallization from ethanol.

N-[2-(2-chlorophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (16)

Yield: 31%, M.p.: 172-174ºC, IR (KBr), ν (cm^{-1}): 3080 (CH aromatic), 3055, 1452 (CH aliphatic), 1715 (C=O), 1595 (N-H), 1390 (C-N), 654 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.88 (s, 6H, 2xCH_3), 6.27 (s, 1H, CH), 6.75-6.79 (dd, 2H, ArH, *J* = 10Hz), 7.12-7.15 (m, 3H, ArH), 7.18-7.21 (m, 1H, ArH), 7.32-7.37 (m, 3H, ArH), 7.68-7.72 (dd, 2H, ArH, *J* = 10Hz), 7.82-7.83 (m, 1H, ArH), 9.81 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 53.2 (CH), 110.4, 121.9, 127.1, 127.7, 127.9, 129.2, 129.4, 129.9, 130.3, 130.4, 131.7, 132.6, 134.8, 136.8, 139.7 152.9 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). Analysis for $C_{23}H_{20}ClN_3O_2S$ (437.94) Calculated: C: 63.08%, H: 4.60%, N: 9.59%, Found: C: 63.11%, H: 4.62%, N: 9.54%.

N-[2-(3-chlorophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (17)

Yield: 28%, M.p.: 164-166ºC, IR (KBr), ν (cm^{-1}): 3065 (CH aromatic), 3048, 1445 (CH aliphatic), 1718 (C=O), 1602 (N-H), 1408 (C-N), 648 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.89 (s, 6H, 2xCH_3), 6.28 (s, 1H, CH), 6.76-6.80 (dd, 2H, ArH, *J* = 10Hz), 7.12-7.23 (m, 4H, ArH), 7.35-7.37 (m, 2H, ArH), 7.46-7.47 (m, 1H, ArH), 7.67-7.71 (dd, 2H, ArH, *J* = 10Hz), 7.80-7.81 (m, 1H, ArH), 9.64 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 56.1 (CH), 110.4, 121.9,

128.6, 128.7, 129.4, 130.3, 130.4, 134.3, 134.8, 136.8, 141.7, 152.9 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). Analysis for $C_{23}H_{20}ClN_3O_2S$ (437.94) Calculated: C: 63.08%, H: 4.60%, N: 9.59%, Found: C: 63.07%, H: 4.58%, N: 9.62%.

N-[2-(4-chlorophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (18)

Yield: 42%, M.p.: 175-177ºC, IR (KBr), ν (cm^{-1}): 3056 (CH aromatic), 3039, 1458 (CH aliphatic), 1709 (C=O), 1611 (N-H), 1410 (C-N), 651 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.90 (s, 6H, 2xCH_3), 6.27 (s, 1H, CH), 6.74-6.78 (dd, 2H, ArH, *J* = 10Hz), 7.18-7.19 (m, 1H, ArH), 7.24-7.27 (dd, 2H, ArH, *J* = 7.5Hz), 7.30-7.33 (dd, 2H, ArH, *J* = 10Hz), 7.38-7.40 (m, 2H, ArH), 7.68-7.72 (dd, 2H, ArH, *J* = 10Hz), 7.82-7.84 (m, 1H, ArH), 9.61 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 54.9 (CH), 110.4, 121.9, 127.1, 129.2, 129.4, 129.5, 129.6, 130.3, 130.4, 133.7, 134.8, 136.8, 138.9, 152.9 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). Analysis for $C_{23}H_{20}ClN_3O_2S$ (437.94) Calculated: C: 63.08%, H: 4.60%, N: 9.59%, Found: C: 63.11%, H: 4.63%, N: 9.57%.

N-[2-(2-bromophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (19)

Yield: 26%, M.p.: 188-190ºC, IR (KBr), ν (cm^{-1}): 3076 (CH aromatic), 3042, 1448 (CH aliphatic), 1718 (C=O), 1620 (N-H), 1401 (C-N), 656 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.90 (s, 6H, 2xCH_3), 6.30 (s, 1H, CH), 6.74-6.78 (dd, 2H, ArH, *J* = 10Hz), 7.10-7.11 (m, 2H, ArH), 7.18-7.20 (m, 2H, ArH), 7.37-7.39 (m, 2H, ArH), 7.48-7.49 (m, 1H, ArH), 7.67-7.71 (dd, 2H, ArH, *J* = 10Hz), 7.81-7.82 (m, 1H, ArH), 9.65 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 53.5 (CH), 110.4, 121.9, 124.3, 127.1, 127.7, 129.2, 129.4, 130.1, 130.3, 130.4, 131.4, 134.8, 136.8, 138.7, 152.9 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). Analysis for $C_{23}H_{20}BrN_3O_2S$ (482.39) Calculated: C: 57.27%, H: 4.18%, N: 8.71%, Found: C: 57.29%, H: 4.20%, N: 8.74%.

N-[2-(3-bromophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (20)

Yield: 54%, M.p.: 155-157ºC, IR (KBr), ν (cm^{-1}): 3052 (CH aromatic), 3038, 1455 (CH aliphatic), 1711 (C=O), 1615 (N-H), 1406 (C-N), 645 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.88 (s, 6H, 2xCH_3), 6.28 (s, 1H, CH), 6.73-6.77 (dd, 2H, ArH, *J* = 10Hz), 7.16-7.19 (m, 3H, ArH), 7.35-7.38 (m, 3H, ArH), 7.62-7.63 (m, 1H, ArH), 7.66-7.70 (dd, 2H, ArH, *J* = 10Hz), 7.80-7.81 (m, 1H, ArH), 9.61 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 56.1 (CH), 110.4, 121.9, 123.4, 127.4, 129.4, 129.7, 130.3, 130.4, 130.9, 132.8, 141.9, 152.9 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). Analysis for $C_{23}H_{20}BrN_3O_2S$ (482.39) Calculated: C: 57.27%, H: 4.18%, N: 8.71%, Found: C: 57.26%, H: 4.16%, N: 8.74%.

N-[2-(4-bromophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (21)

Yield: 63%, M.p.: 156-158ºC, IR (KBr), ν (cm^{-1}): 3078 (CH aromatic), 3042, 1457 (CH aliphatic), 1709 (C=O), 1608 (N-H), 1412 (C-N), 651 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.90 (s, 6H, 2xCH_3), 6.29 (s, 1H, CH), 6.72-6.76 (dd, 2H, ArH, *J* = 10Hz), 7.18-7.21 (m, 3H, ArH), 7.35-7.37 (m, 2H, ArH), 7.46-7.48 (m, 2H, ArH), 7.67-7.71 (dd, 2H, ArH, *J* = 10Hz), 7.80-7.81 (m, 1H, ArH), 9.59 (s, 1H, ArH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 54.9 (CH), 110.4, 121.9, 122.3, 127.1, 129.2, 129.4, 130.3, 130.4, 130.9, 132.5, 134.8, 136.8, 139.5, 152.9 (18Car), 162.3 (C=O), 163.9 (C=O). MS m/z (%): 482 (M^+, 0.55). Analysis for $C_{23}H_{20}BrN_3O_2S$ (482.39) Calculated: C: 57.27%, H: 4.18%, N: 8.71%, Found: C: 57.31%, H: 4.16%, N: 8.73%.

N-[2-(2-fluorophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (22)

Yield: 32%, M.p.: 122-124ºC, IR (KBr), ν (cm^{-1}): 3068 (CH aromatic), 3042, 1458 (CH aliphatic), 1710 (C=O), 1605 (N-H), 1402 (C-N), 642 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.87 (s, 6H, 2xCH_3), 6.27 (s, 1H, CH), 6.75-6.79 (dd, 2H, ArH, *J* = 10Hz), 7.01-7.04 (m, 2H, ArH), 7.13-7.15 (m, 1H, ArH), 7.18-7.20 (m, 2H, ArH), 7.36-7.39 (m, 2H, ArH), 7.68-7.72 (dd, 2H, ArH, *J* = 10Hz), 7.81-7.82 (m, 1H, ArH), 9.58 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 53.3 (CH), 110.4, 117.7, 121.9, 127.1, 129.1, 129.2, 129.4, 130.3, 130.4, 134.8, 136.8, 152.9, 150.2 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). Analysis for $C_{23}H_{20}FN_3O_2S$ (421.49) Calculated: C: 65.54%, H: 4.78%, N: 9.97%, Found: C: 65.57%, H: 4.75%, N: 9.98%.

N-[2-(3-fluorophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (23)

Yield: 41%, M.p.: 120-122ºC, IR (KBr), ν (cm^{-1}): 3055 (CH aromatic), 3032, 1456 (CH aliphatic),

1714 (C=O), 1611 (N-H), 1395 (C-N), 651 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.88 (s, 6H, 2xCH_3), 6.30 (s, 1H, CH), 6.74-6.78 (dd, 2H, ArH *J* = 10Hz), 6.95-6.99 (m, 2H, ArH), 7.17-7.18 (m, 2H, ArH), 7.25-7.27 (m, 1H, ArH), 7.37-7.30 (m, 2H, ArH), 7.67-7.71 (dd, 2H, ArH, *J* = 10Hz), 7.82-7.83 (m, 1H, ArH), 9.67 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 56.1 (CH), 110.4, 111.4, 115.7, 121.9, 123.4, 127.1, 129.4, 130.3, 130.4, 134.8, 136.8, 140.5, 152.9 (17C_{ar}), 162.3 (C=O), 162.7 (C_{ar}), 163.9 (C=O). Analysis for $C_{23}H_{20}FN_3O_2S$ (421.49) Calculated: C: 65.54%, H: 4.78%, N: 9.97%, Found: C: 65.58%, H: 4.81%, N: 9.95%.

N-[2-(4-fluorophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (24)

Yield: 47%, M.p.: 114-116ºC, IR (KBr), ν (cm^{-1}): 3048 (CH aromatic), 3040, 1451 (CH aliphatic), 1719 (C=O), 1620 (N-H), 1390 (C-N), 656 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.89 (s, 6H, 2xCH_3), 6.31 (s, 1H, CH), 6.73-6.77 (dd, 2H, ArH, *J* = 10Hz), 7.02-7.04 (m, 2H, ArH), 7.18-7.20 (m, 2H, ArH), 7.28-7.29 (m, 1H, ArH), 7.37-7.40 (m, 2H, ArH), 7.67-7.71 (dd, 2H, ArH, *J* = 10Hz), 7.81-7.82 (m, 1H, ArH), 9.63 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 54.9 (CH), 110.4, 115.9, 121.9, 127.1, 129.2, 129.4, 130.3, 130.4, 134.8, 136.2, 136.8, 152.9 (17C_{ar}), 162.3 (C=O), 163.9 (C_{ar}), 166.5 (C=O). MS m/z (%): 421 (M^+, 0.74). Analysis for $C_{23}H_{20}FN_3O_2S$ (421.49) Calculated: C: 65.54%, H: 4.78%, N: 9.97%, Found: C: 65.57%, H: 4.76%, N: 9.96%.

N-[2-(2-chloro-6-fluorophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino) benzamide (25)

Yield: 24%, M.p.: 150-152°C, IR (KBr), ν (cm^{-1}): 3089 (CH aromatic), 3065, 1456 (CH aliphatic), 1713 (C=O), 1605 (N-H), 1412 (C-N), 653 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.90 (s, 6H, 2xCH_3), 6.27 (s, 1H, CH), 6.75-6.79 (dd, 2H, ArH, *J* = 10Hz), 6.94-6.95 (m, 1H, ArH), 7.05-7.07 (m, 1H, ArH), 7.14-7.16 (m, 1H, ArH), 7.18-7.19 (m, 1H, ArH), 7.37-7.40 (m, 2H, ArH), 7.66-7.70 (dd, 2H, ArH, *J* = 10Hz), 7.80-7.82 (m, 1H, ArH), 9.57 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 49.0 (CH), 110.4, 117.2, 121.9, 127.1, 129.2, 129.4, 130.3, 130.4, 134.8, 135.22, 136.8, 152.93, 159.64 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). Analysis for $C_{23}H_{19}ClFN_3O_2S$ (455.93) Calculated: C: 60.59%, H: 4.20%, N: 9.22%, Found: C: 60.64%, H: 4.22%, N: 9.24%.

N-[2-(3-bromo-4-methoxyphenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (26)

Yield: 43%, M.p.: 186-188ºC, IR (KBr), ν (cm^{-1}): 3038 (CH aromatic), 3010, 1459 (CH aliphatic), 1719 (C=O), 1613 (NH), 1411 (C-N), 654 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.90 (s, 6H, 2xCH_3), 3.77 (s, 3H, CH_3), 6.30 (s, 1H, CH), 6.74-6.78 (dd, 2H, ArH, *J* = 10Hz), 6.82-6.84 (m, 1H, ArH), 7.18-7.20 (m, 1H, ArH), 7.29-7.31 (m, 2H, ArH), 7.37-7.43 (m, 2H, ArH), 7.67-7.71 (dd, 2H, ArH, *J* = 10Hz), 7.81-7.83 (m, 1H, ArH), 9.62 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 56.1 (CH), 56.8 (CH_3), 110.4, 111.6, 114.8, 121.9, 126.8, 127.1, 129.2, 129.4, 130.3, 130.4, 134.8, 138.5, 152.9, 160.2 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). Analysis for $C_{24}H_{22}BrN_3O_3S$ (512.42) Calculated: C: 56.25%, H: 4.33%, N: 8.20%, Found: C: 56.27%, H: 4.31%, N: 8.22%.

N-[2-(3-bromo-4-hydroxyphenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (27)

Yield: 48%, M.p.: 136-138°C, IR (KBr), ν (cm^{-1}): 3611 (O-H), 3058 (CH aromatic), 3015, 1462 (CH aliphatic), 1719 (C=O), 1614 (NH), 1409 (C-N), 649 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.91 (s, 6H, 2xCH_3), 6.32 (s, 1H, CH), 6.69-6.70 (m, 1H, ArH), 6.74-6.78 (dd, 2H, ArH, *J* = 10Hz), 7.15-7.18 (m, 2H, ArH), 7.30-7.32 (m, 1H, ArH), 7.37-7.39 (m, 2H, ArH), 7.67-7.71 (dd, 2H, ArH, *J* = 10Hz), 7.81-7.83 (m, 1H, ArH), 8.16 (s, 1H, OH), 9.60 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 56.1 (CH), 110.1, 110.4, 116.2, 121.9, 127.6, 129.4, 130.3, 130.4, 133.9, 134.8, 136.8, 137.5, 152.9, 155.2 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). Analysis for $C_{23}H_{20}BrN_3O_3S$ (498.39) Calculated: C: 55.43%, H: 4.04%, N: 8.43%, Found: C: 55.46%, H: 4.03%, N: 8.46%.

N-[2-(5-bromo-2-hydroxyphenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino) benzamide (28)

Yield: 34%, M.p.: 110-112ºC, IR (KBr), ν (cm^{-1}): 3608 (O-H), 3089 (CH aromatic), 3014, 1456 (CH aliphatic), 1711 (C=O), 1614 (N-H), 1403 (C-N), 645 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.92 (s, 6H, 2xCH_3), 6.29 (s, 1H, CH), 6.67-6.68 (m, 1H, ArH), 6.75-6.79 (dd, 2H, ArH, *J* = 10Hz), 7.18-7.20 (m, 1H, ArH), 7.23-7.24 (m, 1H, ArH), 7.27-7.29 (m, 1H, ArH), 7.36-7.39 (m, 2H, ArH), 7.64-7.68 (dd, 2H, ArH), 7.81-7.83 (m, 1H, ArH), 8.26 (s, 1H, OH), 9.80 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 51.2 (CH), 110.4, 112.4, 120.0, 121.9, 127.1, 127.7, 129.2,

129.4, 130.3, 130.4, 130.8. 131.6, 134.8, 136.8, 149.5, 152.9 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). Analysis for $C_{23}H_{20}BrN_3O_3S$ (498.39) Calculated: C: 55.43%, H: 4.04%, N: 8.43%, Found: C: 55.42%, H: 4.05%, N: 8.45%.

N-[2-(2-bromo-3-fluorophenyl)-4-oxo-2*H*-1,3-benzothiazin-3(4*H*)-yl]-4-(dimethylamino)benzamide (29)

Yield: 39%, M.p.: 176-178ºC, IR (KBr), ν (cm^{-1}): 3085 (CH aromatic), 3055, 1458 (CH aliphatic), 1714 (C=O), 1602 (N-H), 1413 (C-N), 654 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.88 (s, 6H, 2xCH_3), 6.32 (s, 1H, CH), 6.75-6.79 (dd, 2H, ArH, *J* = 10Hz), 6.85-6.88 (m, 2H, ArH), 7.17-7.19 (m, 2H, ArH), 7.36-7.37 (m, 2H, ArH), 7.68-7.72 (dd, 2H, ArH, *J* = 10Hz), 7.82-7.84 (m, 1H, ArH), 9.61 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 54.8 (CH), 108.4, 110.4, 119.6, 121.9, 127.1, 129.2, 129.4, 130.3, 130.4, 134.8, 135.9, 136.8, 152.9 (17C_{ar}), 162.3 (C=O), 162.8 (C_{ar}), 163.9 (C=O). Analysis for $C_{23}H_{19}BrFN_3O_2S$ (500.38) Calculated: C: 55.21%, H: 3.83%, N: 8.40%, Found: C: 55.23%, H: 3.85%, N: 8.41%.

N-[2-(3-chloro-4-methoxyphenyl)-4-oxo-2*H*-1,3-benzothiazine-3(4*H*)-yl]-4-(dimethylamino) benzamide (30)

Yield: 54%, M.p.: 105-107ºC, IR (KBr), ν (cm^{-1}): 3078 (CH aromatic), 3038, 1448 (CH aliphatic), 1721 (C=O), 1613 (N-H), 1415 (C-N), 649 (C-S). ^{1}H NMR (DMSO-d_6) δ (ppm) = 2.90 (s, 6H, 2xCH_3), 3.68 (s, 3H, CH_3), 6.34 (s, 1H, CH), 6.74-6.78 (dd, 2H, ArH, *J* = 10Hz), 6.86-6.89 (m, 1H, ArH), 7.18-7.20 (m, 1H, ArH), 7.24-7.27 (m, 2H, ArH), 7.37-7.40 (m, 2H, ArH), 7.67-7.71 (dd, 2H, ArH, *J* = 10Hz), 7.81-7.82 (m, 1H, ArH), 9.63 (s, 1H, NH). ^{13}C NMR (DMSO) δ (ppm) = 41.9 (2xCH_3), 56.1 (CH), 56.8 (CH_3), 110.4, 111.4, 121.9, 123.22, 126.2, 127.1, 129.2, 129.4, 130.3, 134.4, 134.6, 134.8, 136.8, 152.9, 156.3 (18C_{ar}), 162.3 (C=O), 163.9 (C=O). MS m/z (%): 467 (M^+, 0.95). Analysis for $C_{24}H_{22}ClN_3O_3S$ (467.94) Calculated: C: 61.60%, H: 4.74%, N: 8.98%, Found: C: 61.62%, H: 4.76%, N: 8.96%.

3. RESULTS AND DISCUSSION

The aim of this study was the synthesis and spectral analysis of new 2,3-disubstituted-1,3-benzothiazin-4-one derivatives. In the first step of synthesis hydrazones of 4-(dimethylamino)benzoic acid (1-15) were synthesized by the condensation reaction of 4-(dimethylamino)benzhydrazide with appropriate aromatic aldehydes. New desired 2,3-disubstituted-1,3-benzothiazin-4-one derivatives (16-30) were obtained by the cyclization reaction of *N*-substituted derivatives of 4-(dimethylamino)benzhydrazide (1-15) with thiosalicylic acid in the presence of 1,4-dioxane. The obtained yields of final products (16-30), when 1,4-dioxane was used as a solvent, are rather low. After completion of this work, I am aware to publish a report on the influence of the different solvent on the synthesis and yields of obtained 1,3-benzothiazin-4-ones.

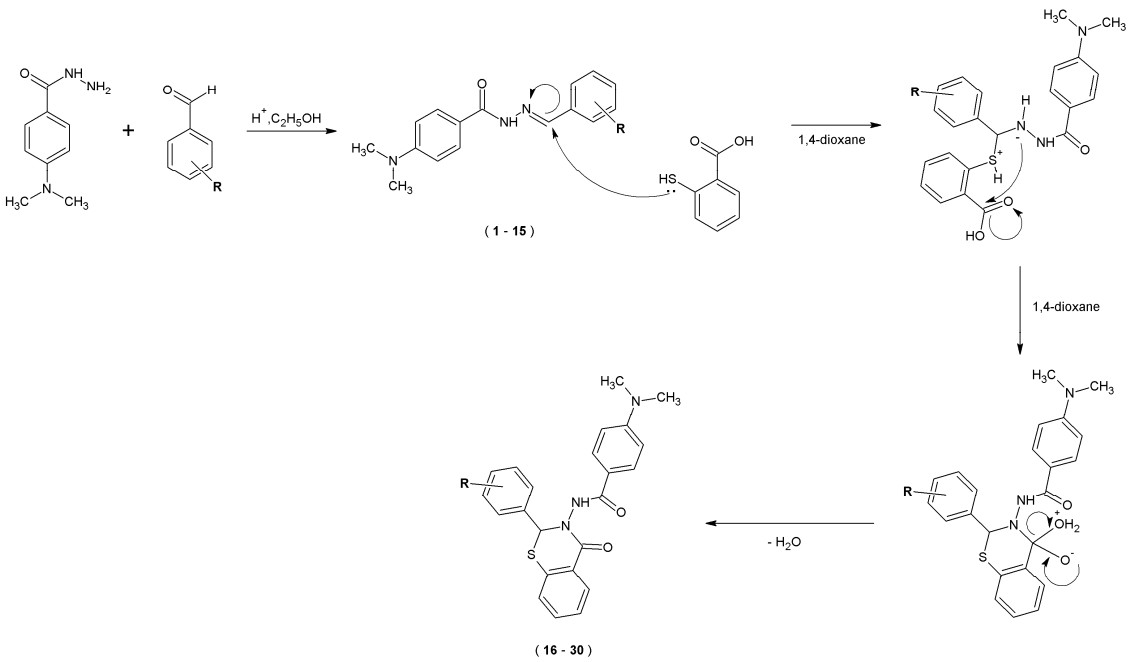
All the spectral (IR, ^{1}H NMR, ^{13}C NMR) data confirmed the successful formation of new compounds (16-30). All synthesized compounds are stable solids and dissolve in DMSO in room temperature.

The IR spectra of synthesized compounds 1-30 confirmed the presence of appropriate functional groups in obtained derivatives. The MS spectra of compounds (21, 24, 30) confirmed the mass of final products.

In the ^{1}H NMR spectra of synthesized hydrazones of 4-(dimethylamino)benzoic acid (1-15) one typical proton singlet signal for =CH group was observed in the range of δ 7.29 – 8.41 ppm and for the NH group at δ 10.49 – 11.82 ppm. Where as in the ^{13}C NMR of compounds 1-15 two signals for =CH and C=O were observed at δ 144.9 – 144.9 ppm and δ 164.1 – 164.3 ppm, respectively what successfully confirmed the formation of expected products. All other aliphatic and aromatic signals were found at usual regions.

In the ^{1}H NMR spectra of 1,3-benzothiazin-4-one derivatives (16-30) the signals for CH and NH groups appeared in the range of δ 6.27 – 6.34 ppm and δ 9.57 – 9.81 ppm, respectively. In the ^{13}C NMR spectra of these target compounds 16-30 the typical signals for CH group at about δ 54 ppm and two C=O groups at about δ 163 ppm were observed. All other aliphatic and aromatic signals were reported at expected regions.

The plausible mechanism of the formation of new 1,3-benzothiazin-4-one derivatives is presented on the Scheme 2. and it was based on the mechanism of the formation of 1,3-thiazolidin-4-ones [14]. The target 1,3-benzothiazin-4-one derivatives (16-30) were synthesized via the route outlined in Scheme 2.



Compound no	R	Compound no	R
1, 16	2-Cl	9, 24	4-F
2, 17	3-Cl	10, 25	2-Cl-6F
3, 18	4-Cl	11, 26	3-Br-4-OCH_3
4, 19	2-Br	12, 27	3-Br-4-OH
5, 20	3-Br	13, 28	5-Br-2-OH
6, 21	4-Br	14, 29	2-Br-3-F
7, 22	2-F	15, 30	3-Cl-4-OCH_3
8, 23	3-F		

Scheme 2. Reactions with plausible mechanism leading to new 1,3-benzothiazin-4-one derivatives (16 - 30)

4. CONCLUSION

In this paper 15 new 2,3-disubstituted derivatives of 1,3-benzothiazin-4-one (16-30) were synthesized via cyclization reaction of *N*-substituted derivatives of 4-(dimethylamino) benzhydrazide (1-15) with thiosalicylic acid. The chemical structure of all synthesized compounds was confirmed by spectral analysis.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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