Convenient synthesis and characterization of some novel benzothiazolone-based Schiff bases as potential pharmaceutically active agents

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Abstract: A novel series of Schiff bases derivatives containing the benzothiazolone moiety have been synthesized in a simple and efficient method, by condensation of 6-amino-2(3H)-benzothiazolone substrates with different aromatic aldehydes, in refluxing ethanol and in the presence of acetic acid as catalyst. The structure of synthesized compounds was elucidated and has been proven using spectral methods such as $^1$H NMR, $^{13}$C NMR and elemental analysis. All the newly synthesized compounds were in good agreement with the proposed structures.

Keywords: Schiff bases; 2(3H)-benzothiazolone; 6-amino-2(3H)-benzothiazolones; aromatic aldehydes. © 2017 ACG Publications. All rights reserved.

1. Introduction

Organic compounds with a general formula $R^1R^2C=NR^3$ are known as Schiff bases, which are usually synthesized from the condensation of primary amines with compounds having active carbonyl groups, in different conditions and in different solvents with the elimination of water molecule. Schiff bases are used as a key intermediate for the synthesis of nitrogen heterocyclic compounds. They play important roles in both synthetic and structural research because of their preparative simplicity and structural diversity. Several synthetic methods have been reported for their synthesis in the literature. Moreover, the Schiff base derivatives have been extensively studied because of their numerous applications in various fields of chemistry and industry. Also, they are reported to possess diverse pharmacological activities.

In addition, benzothiazolone containing heterocycles systems have been incorporated into a wide variety of therapeutically interesting drug candidates. Previous works were published, expanding the structure activity relationship of 6-benzoyl-2(3H)-benzothiazolone (S-14080) as an analgesic compound. 6-benzoyl-2(3H)-benzothiazolone and 6-benzoyl-2(3H)-benzoxazolone also served as lead structures in the design of antiviral compounds, particularly targeted against HIV and CMV species. Furthermore, in recent years, several potentially useful bioactive substances based on the benzothiazolone nucleus have been extensively studied because of their wide range of pharmacological activities, and were reported as potential analgesic and anti-inflammatory agents.

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All the facts discussed above and in continuation of our research on nitrogen and sulfur containing heterocycles, inspired us to develop an efficient and simple synthesis of a new series of benzothiazolone derived Schiff’s base derivatives (Figure 1), which may exert potent pharmacological action.

![Chemical Structure](image)

**Figure 1. Proposed chemical structure of the Schiff base ligands 5a-l**

The present investigation is of interest in synthetic organic chemistry because it is based on the fact that, the chemistry of benzothiazolinononyl Schiff bases derivatives is less explored compared to that of either Schiff bases or benzothiazolone.

2. Experimental

Melting points have been determined using a SMP3 Stuart Scientific apparatus and are uncorrected. The 1H NMR spectra were performed in solutions on a Bruker AC 400 spectrometer using dimethylsulfoxide-d_6 as solvent with TMS as internal standard, with chemical shifts reported as δ (ppm). Analytical thin layer chromatography was performed with commercial silica gel plates 60 F_254 (Merck) and visualized with UV light, using Ethylacetate/Cyclohexane (8:2, v/v) solvent system as eluent. The experimental microanalyses were in satisfactory agreement and were found within 0.4% of the calculated values. The identity of the known products 2(3H)-benzothiazolone derivatives 1, 2, 3a, 3b, 4a and 4b was confirmed by the comparison of their melting points and spectroscopic data with those of authentic compounds available in the literature. 35-40

**General procedure for the preparation of nitro compounds (3a-3b):**

Nitric acid (68%, 5.30 cm^3, 80 mmol) in 20 cm^3 of acetic anhydride cooled to -0.5°C was added dropwise, a solution of 2(3H)-benzothiazolone compounds 1 and 2 (10 mmol) in a minimum of acetic anhydride. The mixture was stirred at -0.5°C for 3 h. The precipitate was filtered, washed with cold water, dried and recrystallized from suitable solvent to afford the corresponding 6-nitrobenzothiazolones compounds 3a (56%) and 3b (68%).

**General procedure for the preparation of amino compounds (4a-4b):**

To a stirring ethanolic solution of 6-nitro-2(3H)-benzothiazolone (4a) or 3-methyl-6-nitro-2(3H)-benzothiazolone (4b) (1.0 equiv.) in a 250 ml round bottomed flask, tin chloride dihydrate (SnCl_2·H_2O, 5 equiv.) was added. The reaction mixture was heated at reflux and reaction continued until completion of the reaction (TLC monitoring). After complete reduction, the starting material disappeared, and the solution was allowed to cool down. The pH was made slightly basic (pH 7–8) by addition of 5% aqueous sodium bicarbonate before extraction with ethyl acetate. The organic phase was washed with brine and dried over magnesium sulfate, and the solvent was removed. The solid 6-aminobenzothiazolone intermediates 4a (68%) and 4b (67%), were obtained after being washed with petroleum ether, and used for the next step without further purification.

**General procedure for the preparation of Schiff bases ligands (5a-5l):**

The Schiff base ligands were prepared by condensation of an equimolar mixture of substituted aromatic aldehydes and 6-aminobenzothiazolones (4a-4b), in an ethanolic solution and in presence of catalytic amount of glacial acetic acid under nitrogen atmosphere. Then, the resulting mixture was heated at reflux for 0.5h until the completion of the reaction (TLC monitoring). The solid product thus obtained was filtered, washed several times with ethanol and cold water, dried and purified to give the desired products (5a-5l). All prepared products were obtained following the general procedure under heat at reflux for 0.5h, as coloured solid products with yield (64-90%). On the
basis of various analytical and NMR spectroscopic data which are given in the experimental section, the structure for the compounds has been proposed (Figure 1).

**Physicochemical and spectral data of new products: 6-(Arylideneamino)benzo[d]thiazol-2(3H)-one derivatives (5a-5l):**

6-(2-cyanobenzylideneamino)benzo[d]thiazol-2(3H)-one (5a): Yellow powder (75%); m.p. 226-227°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): 7.19 (d, J = 8.4 Hz, 1H), 7.33-7.35 (dd, J1 = 2.0 Hz, 1H), 7.70-7.72 (m, 2H), 7.85 (t, J2 = 8.0 Hz, J3 = 8.0 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.82 (s, N=CH, azomethine, 1H), 12.00 (s, N-H, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 170.0 (C=O), 155.1 (N=C), 145.1, 137.4, 135.6, 134.1, 133.4, 131.5, 128.6, 124.4, 120.7, 117.2, 115.34, 112.0, 111.4. Anal. Calcd for C13H9N2O: C, 64.50; H, 3.25; N, 15.04; S, 11.48. Found: C, 64.44; H, 3.23; N, 15.90; S, 11.39.

3-methyl-6-(2-cyanobenzylideneamino)benzo[d]thiazol-2(3H)-one (5b): Yellow powder (69%); m.p. 189-190°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): 3.44 (s, N-CH3, 3H), 7.40 (d, J = 8.8 Hz, 1H), 7.43-7.46 (dd, J1 = 2.0, J2 = 6.4, 1H), 7.71-7.88 (m, 3H), 7.98-8.01 (dd, J1 = 1.2, J2 = 6.8 Hz, 1H), 8.20 (d, J = 7.6 Hz, 1H), 8.84 (s, N=CH, azomethine, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 168.70 (C=O), 155.5 (N=C), 145.7, 137.3, 136.7, 134.1, 133.4, 131.6, 128.7, 122.3, 120.7, 117.2, 115.4, 111.8, 111.5. 111.8. 29.17 (CH3). Anal. Calcd for C16H14N2O: C, 65.51; H, 3.78; N, 14.34; S, 10.93. Found: C, 64.65; H, 3.23; N, 14.30; S, 10.94.

6-(4-cyanobenzylideneamino)benzo[d]thiazol-2(3H)-one (5c): Yellow powder (90%); m.p. 311-312°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): 7.17 (d, J = 8.4 Hz, 1H), 7.32-7.35 (dd, J1 = 8.0 Hz, J2 = 2.4 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.4 Hz, 2H), 8.79 (s, N=CH, azomethine, 1H), 12.00 (s, N-H, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 169.9 (C=O), 158.0 (N=C), 154.5, 139.9, 135.3, 133.1, 132.7, 129.8, 128.9, 129.4, 123.0, 117.8, 115.3, 111.9, 113.1. Anal. Calcd for C16H13N2O: C, 64.50; H, 3.25; N, 15.04; S, 11.48%. Found: C, 64.22; H, 3.23; N, 15.02; S, 11.35%.

3-methyl-6-(4-cyanobenzylideneamino)benzo[d]thiazol-2(3H)-one (5d): Yellow powder (81%); m.p. 205-206°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): 3.43 (s, N-CH3, 3H), 7.38 (d, J = 8.8 Hz, 1H), 7.42-7.45 (dd, J1 = 8.8 Hz, J2 = 2.0 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 8.08 (s, 1H), 8.10 (s, 1H), 8.81 (s, N=CH, azomethine, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 163.8 (C=O), 157.3 (N=C), 144.6, 140.1, 135.7, 132.7, 131.9, 129.8, 127.4, 122.2, 120.6, 118.6, 115.5, 111.8, 112.0, 29.2 (CH3). Anal. Calcd for C16H13N2O: C, 65.51; H, 3.78; N, 14.34; S, 10.93%. Found: C, 65.62; H, 3.71; N, 14.72; S, 10.18%.

6-(2,4-dimethoxybenzylideneamino)benzo[d]thiazol-2(3H)-one (5e): Yellow powder (66%); m.p. 227-228°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): 3.85 (s, 3H, O-CH3), 3.89 (s, 3H, O-CH3), 6.65 (t, J1 = 8.8 Hz, J2 = 2.0 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.14-7.17 (dd, J = 6.4 Hz, J = 2.0 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 8.8 Hz, 1H), 8.75 (s, 1H, N=CH, azomethine, 11.86 (s, 1H, N-H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 170.0 (C=O), 163.6 (N=C), 160.7, 153.9, 147.3, 134.1, 128.1, 124.2, 120.1, 117.1, 114.7, 111.8, 106.5, 98.0, 55.8 (OCH3), 55.5 (OCH3). Anal. Calcd for C16H14N2O3S: C, 61.13; H, 4.49; N, 8.91; S, 10.20%. Found: C, 59.60; H, 4.40; N, 8.76; S, 9.76%.

3-methyl-6-(2,4-dimethoxybenzylideneamino)benzo[d]thiazol-2(3H)-one (5f): Yellow powder (73%); m.p. 177-178°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): 3.41 (s, N-CH3, 3H), 3.87 (s, 3H, O-CH3), 3.89 (s, 3H, O-CH3), 6.64-6.68 (m, 2H), 7.24-7.27 (dd, J1 = 2.0, J2 = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 8.779 (s, N=CH, azomethine, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 168.6 (C=O), 163.6 (N=C), 160.7, 154.3, 147.9, 135.4, 128.1, 122.1, 120.2, 117.0, 114.7, 111.6, 106.5, 98.0, 55.8 (OCH3), 55.5 (OCH3). Anal. Calcd for C16H14N2O3S: C, 62.18; H, 4.91; N, 8.53; S, 9.76%. Found: C, 62.18; H, 4.91; N, 8.83; S, 9.38%.
6-(2,5-dimethoxybenzylideneamino)benzo[d]thiazol-2(3H)-one (5g): Yellow powder (72%); m.p. 196-197°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): δ 7.77 (s, 3H, O-CH3), 3.85 (s, 3H, O-CH3), 7.11 (m, 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.21 (dd, J1 = 6.4, J2 = 2.0 Hz, 1H), 7.52 (t, J1 = 3.2, J2 = 2.0, 1H), 7.56 (d, J = 2.0 Hz, 1H), 8.48 (s, N=CH, azomethine, 1H), 11.92 (s, N-H, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 170.0 (C=O), 154.2 (N=C), 153.7, 153.1, 147.6, 134.6, 124.4, 124.3, 120.3, 119.4, 114.9, 113.6, 111.8, 110.0, 56.2 (OCH3), 55.4 (OCH3). Anal. Calcd for C16H13N2O5S: C, 61.13; H, 4.49; N, 8.91; S, 10.20%. Found: C, 59.60; H, 4.40; N, 8.76; S, 9.76%.

3-methyl-6-(2,5-dimethoxybenzylideneamino)benzo[d]thiazol-2(3H)-one (5h): Yellow powder (83%); m.p. 165-166°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): 3.42 (s, N-CH3, 3H), 3.78 (s, O-CH3, 3H), 3.85 (s, O-CH3, 3H), 7.11 (s, 1H), 7.12 (s, 1H), 7.33 (s, 1H), 7.32 (d, J = 1.6 Hz, 2H), 7.53 (t, J = 3.2 Hz, J2 = 1.6, 1H), 7.66 (d, J = 1.6 Hz, 1H), 8.86 (s, N=CH, azomethine, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 168.6 (C=O), 154.6 (N=C), 153.8, 153.1, 147.2, 135.9, 124.3, 122.2, 120.4, 119.5, 114.9, 113.6, 111.7, 110.0, 56.2 (OCH3), 55.4 (OCH3), 29.0 (CH3). Anal. Calcd for C16H13N2O5S: C, 62.18; H, 4.91; N, 8.53; S, 9.76%. Found: C, 62.36; H, 5.01; N, 8.26; S, 9.44%.

6-(2-chloro-6-nitrobenzylideneamino)benzo[d]thiazol-2(3H)-one (5i): Yellow powder (65%); m.p. 232-233°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): 7.16 (d, J = 8.4 Hz, 1H4), 7.20-7.23 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.73 (t, J1 = 8.0 Hz, J2 = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.88 (s, N=CH, azomethine, 1H), 12.01 (s, N-H, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 170.2 (C=O), 153.2 (N=C), 149.7, 144.8, 135.2, 133.0, 123.2, 124.4, 120.5, 119.3, 119.1, 116.5, 115.3, 112.1. Anal. Calcd for C14H15ClN3O5S: C, 50.38; H, 2.42; N, 12.59; S, 9.61%. Found: C, 50.40; H, 2.40; N, 12.54; S, 9.47%.

3-methyl-6-(2-chloro-6-nitrobenzylideneamino)benzo[d]thiazol-2(3H)-one (5j): Yellow powder (75%); m.p. 202-203°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): 3.43 (s, 3H, N-CH3), 7.31-7.33 (dd, J1 = 6.8 Hz, J2 = 2.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 1.6 Hz, 1H), 7.75 (t, J1 = 8.0 Hz, J2 = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 8.92 (s, N=CH, azomethine, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 168.7 (C=O), 153.5 (N=C), 152.7, 149.5, 145.1, 137.0, 134.5, 133.9, 133.7, 132.1, 127.7, 123.2, 120.4, 115.3, 111.8, 29.1 (CH3). Anal. Calcd for C13H10ClN3O5S: C, 51.80; H, 2.90; N, 12.08; S, 9.22%. Found: C, 51.55; H, 2.88; N, 12.44; S, 9.03%.

6-(4-(methylthio)benzylideneamino)benzo[d]thiazol-2(3H)-one (5k): Yellow powder (64%); m.p. 220-221°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): 3.32 (s, 3H, S-CH3), 7.14 (d, J = 8.4 Hz, 1H), 7.23-7.26 (dd, J1 = 8.4 Hz, J2 = 2.0 Hz, 1H), 7.37 (s, 1H), 7.39 (s, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.83 (s, 1H), 859 (s, 1H), 8.61 (s, N=CH, azomethine, 1H), 11.92 (s, N-H, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 169.9 (C=O), 158.9 (N=C), 146.3, 142.7, 134.5, 132.5, 128.9 (2C), 125.3 (2C), 124.2, 120.4, 114.9, 111.8, 14.1 (S-CH3). Anal. Calcd for C15H15N2O2S: C, 59.97; H, 4.03; N, 9.33; S, 21.35%. Found: C, 59.31; H, 3.99; N, 8.94; S, 21.02%.

3-methyl-6-(4-(methylthio)benzylideneamino)benzo[d]thiazol-2(3H)-one (5l): Yellow powder (75%); m.p. 157-158°C. 1H NMR (400 MHz, DMSO-d6, δ ppm): δ 5.32 (s, 3H, N-CH3), 5.43 (s, 3H, S-CH3), 9.59-9.40 (m, 4H), 9.67 (s, 1H), 9.85 (d, J = 2Hz, 1H), 9.87 (d, J = 1.6 Hz, 1H), 10.64 (s, N=CH, azomethine, 1H). 13C NMR (100 MHz, DMSO-d6, δ ppm): 168.5 (C=O), 159.3 (N=C), 146.8, 142.8, 135.8, 132.4, 128.9, 125.3, 121.1, 120.3, 115.1, 111.7, 29.1 (N-CH3), 14.1 (S-CH3). Anal. Calcd for C15H15N2O2S: C, 61.12; H, 4.49; N, 8.91; S, 20.40. Found: C, 61.01; H, 4.46; N, 9.25; S, 20.36.

3. Results and Discussion

In this work, we have developed a facile and efficient approach for the synthesis of some novel Schiff bases compounds containing the benzothiazolone moiety. The reaction of the starting compounds 6-amino-2(3H)-benzothiazolones 4a and 4b with substituted benzaldehyde derivatives in ethanol and acetic acid under conventional heating method was studied.
The synthesis of the desired Schiff base 6-(arylideneamino)benzo[d]thiazol-2(3H)-one derivatives (5a-l) was accomplished according to the steps illustrated in the schemes below. The compound, 3-methyl-2(3H)-benzothiazolone (2) was prepared by methylation using dimethylsulfate and sodium hydroxide in aqueous medium of 2(3H)-benzothiazolone (1), which was readily synthesized via the reaction of 2-aminothiophenol and urea (Scheme 1).

**Scheme 1.** Reagents and conditions: (a) Δ, 160°C, 3h; (b) dimethylsulfate, NaOH, 2h

The 2(3H)-benzothiazolone (1) and 3-methyl-2(3H)-benzothiazolone (2) were then converted to 6-nitro-2(3H)-benzothiazolone (3a) and 3-methyl-6-nitro-2(3H)-benzothiazolone (3b) derivatives, by a nitration reaction of the aromatic ring of compounds 1 and 2 with nitric acid in acetic anhydride. The nitro group of compounds 3a-3b was reduced by the tin chloride dihydrate (SnCl₂·2H₂O) in refluxing ethanol, yielded the intermediates substrates 6-amino-2(3H)-benzothiazolones 4a and 4b respectively (Scheme 2).

**Scheme 2.** Reagents and conditions: (c) HNO₃ (68%), acetic anhydride, -5-0°C; (d) SnCl₂·2H₂O, ethanol, reflux, 3h

The final step was performed by condensing 4a and 4b with different aromatic aldehydes at refluxing ethanol, in the presence of catalytic amount of glacial acetic acid. This process yielded 64-90% of the pure desired products (Scheme 3). On the basis of various analytical and NMR spectroscopic data which are given in the experimental section, the structure for the compounds has been proposed (Figure 1).

**Scheme 3.** Reagents and conditions: (e) appropriate aldehydes, glacial acetic acid, absolute ethanol, reflux, 30 min

All syntheses of the benzothiazolone-based Schiff base derivatives were completed within 30 min. The physical data and yield of the newly synthesized compounds are summarized in the table 1.

4. Conclusion

In summary, this present study reports an efficient strategy and a successful synthesis of a series of novel Schiff base containing benzo[d]thiazol-2(3H)-one nucleus in good yields, by reaction of 6-amino-2(3H)-benzothiazolone intermediates with various aromatic aldehydes in ethanol and a catalytic amount of glacial acetic acid under reflux conditions. The structural characterizations of the
title compounds were confirmed by using the $^1$H NMR, $^{13}$C NMR, spectral technique and elemental analysis. The employed analytical methods confirmed the structures of the obtained compounds, for both the intermediates and the final products. Finally, it can be concluded that different substituent’s on aromatic nucleus influences the activity, and the synthesized Schiff bases products could represent a group of potential agents for the development of new bioactive compounds.

**Table 1.** Physicochemical data of the synthesized compounds 5a-5l

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<th>R</th>
<th>R'</th>
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<td>30</td>
<td>75</td>
<td>C$<em>{16}$H$</em>{14}$N$_{2}$OS$_2$</td>
</tr>
</tbody>
</table>

$^a$Melting point; $^b$Isolated yield after silica chromatography

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**References**


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