Synthesis, Characterization and Antibacterial Evaluation of Some Arylideneaminotetrahydrobenzothiazoles

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Abstract

The starting material, 2-amino-4,5,6,7-tetrahydrobenzo[d]thiazole (1), was prepared from cyclohexanone and thiourea in the presence of iodine under heating on a water bath with occasional stirring. Reaction of 2-amino-4,5,6,7-tetrahydrobenzo[d]thiazole (1) with various aromatic aldehydes afforded 2-arylideneamino-4,5,6,7-tetrahydrobenzo[d]thiazole derivatives (2-8) in excellent yields. The structures of the synthesized thiazole derivatives have been established on the basis of their IR, NMR spectral data and elemental analyses. The obtained compounds were screened for their antibacterial activities against three Gram-positive pathogenic organisms: Bacillus cereus (BTCC 19), Bacillus subtilis (BTCC 17), Staphylococcus aureus (ATCC 6538) and against six Gram-negative pathogenic organisms: Shigella dysenteriae (AE 14396), Salmonella typhi (AE 14612), Pseudomonous aeruginosa, Vibrio cholerae, Escherichia coli (ATCC 25922) and Salmonella paratyphi. The disc diffusion method was used for antibacterial activities. Some of them were found to possess significant activity, when compared to standard drug.

Keywords: Aminothiazole, Arylideneaminothiazole, Antibacterial Activity

1. Introduction

Heterocyclic compounds are widely distributed in nature and occupy a prominent place in medicinal chemistry as pharmaceuticals and drug intermediates (Brown, 1984 and Petrie et al, 1985). They play a significant role in the metabolism of all living cells and many are clinical use for the treatment of various diseases. The search for biologically active substances led us to the investigation of condensed sulfur- and nitrogen-containing heterocycles. Thiazoles are very similar to such skeletons, which are present in many compounds possessing biological activity (Mathew et al, 2009). Thiazole template is a privileged structure fragments in modern medicinal chemistry considering its broad pharmacological spectrum and affinity for various bio-targets of these class heterocyclic compounds. It is among the usually occurred heterocyclic nuclei in many marine as well as natural plant products possessing the wide range of biological applications (Hosseim, 2006). Thiazole derivatives display a wide range of biological activities such as cardiotonic fungicidal, sedative, anesthetic, bactericidal and anti-inflammatory (Theophil, 2003). Some of thiazole derivatives, especially 2-aminothiazoles, possessed antiviral (Ghaemmaghami et al, 2010), antimicrobial (Siddiqui et al, 2007), anticancer (Bang et al, 2010), antiulcer (Ibrahim et al, 2010), anti-inflammatory (Pei et al, 2009) effects. Aminothiazoles and related heterocycles represent a novel class of potent and selective antitumor agents which exhibit nanomolar inhibitory activity against a range of human breast, leukemia, lung, colon, CNS, melanoma, ovarian, renal and prostate cell lines in vitro (Kayagil et al, 2009).

The therapeutic importance of heterocycles has generated much interest in the synthesis of new classes of heterocyclic systems in order to explore their biodynamic properties. Encouraged by these observations and in continuation of search for antimicrobial active molecules (Bhuiyan et al, 2005, 2006, 2011 a, b, and 2012), it was decided to synthesize some thiazole derivatives in order to evaluate their antibacterial activities.
2. Experimental

2.1. Physical Measurements

Melting points were recorded with electro thermal melting point apparatus and were uncorrected. Evaporation of solvents was performed under reduced pressure on a Buchi rotator evaporator. Thin layer chromatography was performed on Kieselgel GF254 and visualization was accomplished by iodine vapour or UV Flame. 1H- and 13C-NMR (270.05 MHz and 67.80 MHz) spectra were recorded on a Varian spectrometer in CDCl3 or DMSO-d6 solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and J values were given in Hz. The carbon, hydrogen and nitrogen percentages in synthesized products were analyzed according to the approved method ASTM D-5291 by employing Leco-CHNS-932 analyzer.

2.2. Synthesis of 2-amino-4,5,6,7-tetrahydrobenzo[d]thiazole (1)

Thiourea (200 mmol) and iodine (200 mmol) were triturated and mixed with cyclohexanone (100 mmol). The mixture was heated on a water bath with occasional stirring for about 10 hours. The conversion was checked by TLC (ethylacetate: n-hexane, 1:5, v/v) on silica gel which showed conversion of starting material into one moving faster product. The obtained solid was triturated with diethyl ether solution to remove unreacted cyclohexanone. Then washed with aqueous sodium thiosulphate solution to remove excess of iodine and then with water. The crude product was dissolved in hot water, filter to remove sulphone and required 2-amino-4,5,6,7-tetrahydrobenzo[d]thiazole (1) was precipitated by addition of NH4Cl. Recrystallised from ethanol gave the white solid crystals yield about 85% and m.p. was 188-190 °C.

IR (KBr): nu max 3064.68, 2925.81, 1697.24, 1591.16, 1539.09 cm⁻¹. 1H-NMR (270.05 MHz, CDCl3): δ 9.31 (s, 1H, =CH, benzylidine), 8.30 (d, 1H, aromatic, J=7.02 Hz), 7.41 (m, 2H, aromatic), 7.33 (m, 1H, aromatic), 2.79 (m, 4H, 2×CH2), 1.88 (t, 4H, 2×CH2, J=2.97 Hz). 13C-NMR (67.80 MHz, CDCl3): δ 168.80, 158.14, 149.41, 136.85, 132.96, 132.41, 130.04, 129.09, 129.02, 127.12, 26.79, 23.83, 23.22, 22.93. Analysis calculated for C14H13N3S: C 67.26, H 6.37, N 14.72, S 11.23; Found: C 67.26, H 6.37, N 14.72, S 11.23.

2.3. General Procedure for 2-arylideneamino-4,5,6,7-tetrahydrobenzo[d]thiazole (2-6)

An equimolecular mixture of compound 1 and aromatic aldehyde was dissolved in ethanol and refluxed for 6 hours. After complete conversion of the reaction (TLC; ethyl acetate: n-hexane; 1:5, v/v), the solvent was evaporated under reduced pressure. The obtained solid mass was recrystallized from ethyl acetate and n-hexane solvent mixture.

2.3.1. Spectral Data
2×CH, aromatic, $J=8.64$ Hz), 2.78 (m, 4H, 2×CH$_2$), 2.35 (s, 3H, CH$_3$), 1.82 (m, 4H, 2×CH$_2$). $^{13}$C-NMR (67.80 MHz, CDCl$_3$): δ 165.80, 156.81, 149.10, 138.33, 129.79, 129.60, 128.60, 128.27, 128.11, 128.00, 26.78, 23.80, 23.42, 22.92, 20.61. Analysis calculated for C$_{16}$H$_{18}$N$_2$S (256.10): C 70.27, H 6.29, N 10.93, S 12.51; Found: C 70.50, H 6.15, N 11.40, S 12.76.

2-(4-chlorobenzylideneamino)-4,5,6,7-tetrahydrobenzo[d]thiazole (7): yellow crystals, yield 92%, m.p. 98-99 °C. IR (KBr): $\nu$max 3037.68, 2929.67, 1591.16, 1554.52 cm$^{-1}$. $^{1}$H-NMR (270.05 MHz, CDCl$_3$): δ 8.88 (s, 1H, =CH, arylidene), 7.87 (d, 2H, aromatic, $J=8.37$ Hz), 1.89 (m, 4H, 2×CH$_2$). $^{13}$C-NMR (67.80 MHz, CDCl$_3$): δ 168.80, 159.84, 149.15, 138.36, 133.79, 130.68, 130.62, 129.22, 129.16, 129.00, 26.70, 23.81, 23.24, 22.95. Analysis calculated for C$_{16}$H$_{18}$N$_2$SCl (276.79): C 67.10, H 6.34, N 10.12, S 11.58; Found: C 67.30, H 5.89, N 9.39, S 12.40.

2-(4-ethoxybenzylideneamino)-4,5,6,7-tetrahydrobenzo[d]thiazole (8): yellow crystals, yield 90%, m.p. 115-116 °C. IR (KBr): $\nu$max 3037.68, 2929.67, 1591.16, 1554.52 cm$^{-1}$. $^{1}$H-NMR (270.05 MHz, CDCl$_3$): δ 8.82 (s, 1H, =CH, arylidene), 7.88 (d, 2H, aromatic, $J=8.91$ Hz), 6.94 (d, 2H, aromatic, $J=8.91$ Hz), 4.10 (q, 2H, OCH$_2$), 1.88 (m, 4H, 2×CH$_2$). $^{13}$C-NMR (67.80 MHz, CDCl$_3$): δ 168.80, 159.84, 149.15, 138.36, 133.79, 130.68, 130.62, 129.22, 129.16, 129.00, 26.70, 23.81, 23.24, 22.95. Analysis calculated for C$_{21}$H$_{24}$N$_2$SO (286.40): C 67.10, H 6.34, N 9.78, S 11.20; Found: C 70.56, H 7.05, N 10.67, S 12.34.

Table 1. Antibacterial Activity of The Synthesized Compounds (2-8)

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<th>Compound No.</th>
<th>B. cereus</th>
<th>B. subtilis</th>
<th>S. aureus</th>
<th>S. dysenteriae</th>
<th>S. typhi</th>
<th>P. aeruginosa</th>
<th>Vibrio cholerae</th>
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2.4. Antimicrobial Screening

The synthesized compounds (2-8) were screened for antibacterial activity against three Gram-positive pathogenic organisms: Bacillus cereus (BTCC 19), Bacillus subtilis (BTCC 17), Staphylococcus aureus (ATCC 6538), six Gram-negative organisms: Shigella dysenteriae (AE 14396), Salmonella typhi (AE 14612), Pseudomonous aeruginosa, Vibrio cholerae, Escherichia coli (ATCC 25922), Salmonella paratyphi (Table 1). The disc diffusion method (Bauer et al, 1966) was used for antibacterial activities.

The tested compounds were dissolved in N,N-Dimethylformamide (DMF) to get a solution of 1 mg ml$^{-1}$. The inhibition zones were measured in mm at the end of an incubation period of 48 hours at (35±2) °C. DMF alone showed no inhibition. Nutrient agar (NA) and potato dextrose agar (PDA) were used as basal media to test the bacteria and fungi, respectively. Commercial antibacterial Ampicillin was also tested under similar conditions for comparison.

3. Results and Discussion

The starting material, 2-amino-4,5,6,7-tetrahydrobenzo[d]thiazole (compound 1), was prepared from cyclohexanone and thiourea in presence of iodine according to literature procedure (Liu et al, 2000). Refluxing of compound 1 with various aromatic aldehydes in ethanol afforded 2-arylideneamino-4,5,6,7-tetrahydrobenzo[d]thiazoles (2-8) (Scheme 1). The structural assignment of compounds (2-8) was confirmed by spectroscopic analyses and micro analytical data. For example the IR spectrum of compound 8, exhibited characteristic band absorptions for C=N and C=C group at 1620 and 1558.38 cm$^{-1}$ respectively. The $^{1}$H-NMR spectr-
al resonated at δ 8.82 corresponding to =CH proton of arylideneamino group. The spectrum exhibited two doublets signals at δ 7.88 (J=8.91 Hz) and 6.94 (J=8.91 Hz) were attributed to four protons of phenyl ring. The spectrum also displayed one quartet signal at δ 4.10 (J=7.02Hz) and one triplet at δ 1.44 (J=7.02Hz) indicating the presence of -OCH₂CH₃ group. Other peaks were also accordingly assigned with structure. The ¹³C-NMR spectrum of the compound showed the presence of fourteen signals attributed to sixteen carbons corresponding molecular formula C₁₆H₁₈N₂SO. All of the synthesized compounds exhibited signal of a one-proton singlet around at δ 8.82 to 9.74 in their ¹H-NMR spectra for arylideneamino proton (N=CH). ¹³C-NMR and micro analytical data also confirmed the assigned structures (See experimental section).

Most of the compounds showed moderate to good antibacterial activities when compared to standard drug.

4. Conclusion

The present work demonstrated the synthesis of 2-arylideneamino-4,5,6,7-tetrahydrobenzo[d]thiazole derivatives (2-8) in excellent yields. These derivatives can be used as precursors for the preparation of thiazolidin-4-ones, azetidin-2-ones for biological interest. The activity data obtained during the study will be certainly useful to go for further research for drug designing and synthesizing new heterocyclic derivatives.

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