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Synthesis And Spectral Studies Of 7-Chloro-4-(N-Butylamido)-2, 3-Dihydro-1, 4-Benzothiazine And 7-Chloro-4-(N-Butyl-N-Nitrosoamido)-2, 3-Dihydro-1, 4-Benzothiazine

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Abstract

Heterocyclic compounds have been shown significant uses in the field of biochemistry, medicinal Chemistry, agricultural science etc. They are important in the metabolism of all living cells. They are widely used in designing of pharmaceutical drugs as building blocks. An important heterocyclic compound is phenothiazine which is a tricyclic compound having thiazine nucleus, possesses a wide spectrum of biological activities and is significantly active to central nervous system. Phenothiazines also exhibit potential as anticancer agents. They interact with DNA via complexation. Biological activities of phenothiazines have been ascribed to structural specificity due to a fold along nitrogen –sulphur axis. 1, 4-Benzothiazines are important analogs of phenothiazines and structural specificity of a fold along nitrogen-sulphur axis is also present in these compounds. Derivatives of 1, 4-benzothiazines are highly bioactive and have widespread use in various therapeutic medicines. In the present research work the synthesized compounds have 2, 3-dihydro-1 4-benzothiazine nucleus having a side chain at position 4- forming nitrosourea linkage. Anti -cancer activities of some of derivatives of 4-(N-alkyl/ aryl-N-nitrsoamido)-2, 3-dihydro-1, 4-benzothiazine derivatives have been reported.[8-9]

Keywords

Phenothiazines, 1, 4-benzothiazines, pharmaceutical drugs, alkylation, complexation, nitrosoureas

Introduction

Nitrosoureas are an interesting class of anti-cancer and immunomodulating drugs due to their unique chemical and biological characteristics. They are used to treat various cancers, including brain tumors, lymphomas and pancreas cancer. Common examples are carmustine (BCNU), streptozotocin, lomustine (CCNU), fotemustine, 2-chloroethyl nitrosourea (CNU), 1, 3-bis (cyclohexyl)-1-nitrosourea (BCyNU), 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) etc. They interact with DNA by alkylation and inhibit cell replication and demage DNA. Lipophilic character of the nitrosoureas is an important property due to which they have the ability to cross the blood-brain barrier whereas many antitumor agents failed to do so. Their clinical use is limited however because of the cumulative and delayed side effects exerted by these

compounds, bone marrow toxicity being dose limiting. Therefore it is worthwhile to develop a series of nitrosoureas with minimum toxicity and side effects. The synthesized compounds contain both 2 3-dihydro-1 4-bezothiazine nucleus and nitrosourea linkage. They will interact with DNA by complexation as well as alkylation.

Synthesis method

5-Chloro-2-(2-aminophenylthio) ethanol (compound 3, fig. 1) synthesized by the reaction of 2-amino-5-chlorobenzenethiol (compound 1, fig.1) with ethylene chlorohydrin.

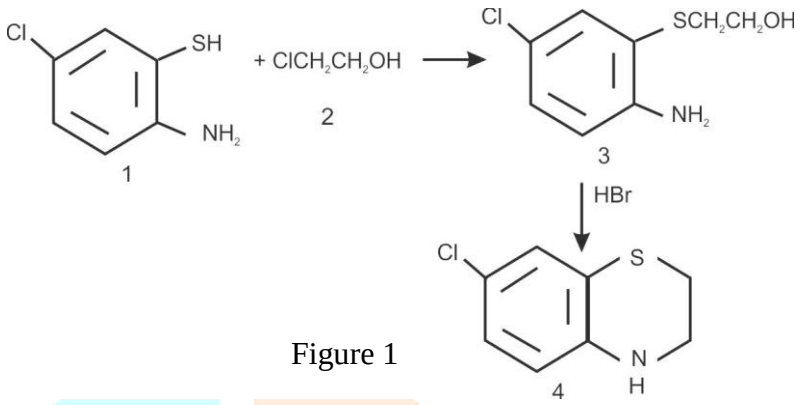

Figure 1

Dehydration of 5-chloro-2-(2-aminophenylthio) ethanol with hydrobromic acid resulted 7-chloro-2, 3-dihydro -1, 4-benzothiazine (compound 4, fig. 1). 7-Chloro-2,3-Dihydro-1,4-benzothiazines converted into 7-chloro-4-(N-butylamido) -2,3-dihydro-1,4-benzothiazine (compound 6, fig.2) by the reaction with butyl isocyanate which on nitrosation with acetic acid and sodium nitrite converted into 7-chloro-4-(N-butyl-N-nitrosoamido)-2,3-dihydo-1,4-benzothiazine (compound 7, figure 2).

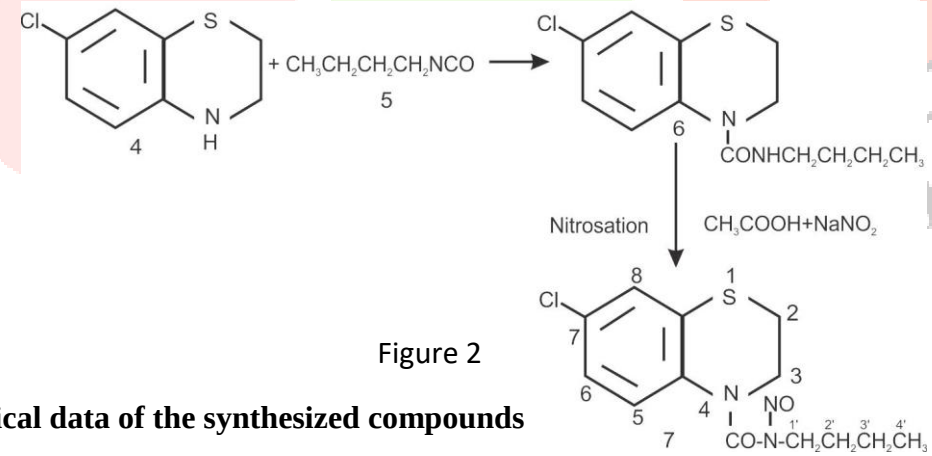

Figure 2

Physical data of the synthesized compounds

Compound 3. 5-Chloro-2-(2-aminophenylthio) ethanol

IR: 3400-3160 cm^{-1} (NH_2 stretching vibrations band overlapped by broad OH stretching vibrations band), 735 cm-1 (C- Cl stretching)

^1H NMR ($CDCl_3$):

δ 7.96-6.99 ppm (multiplet due to 3H aromatic protons), δ 4.55 ppm (singlet due to 3H, NH_2 peak overlapped by OH peak), δ 3.88-3.69 ppm (triplet due to CH_2 protons attached to oxygen), δ 3.44-3.25 ppm (triplet due to CH_2 protons attached to sulphur). Anal. data for $C_8H_{10}NSOCl$: Calcd. C 47.17, H 4.94; Found C 47.38, H 4.91

Compound 4. 7- Chloro-2, 3-dihydro-1, 4-benzothiazine

IR: 3300 cm^{-1} (N-H-stretching), 760 (C- Cl stretching)

^1H NMR ($CDCl_3$)

δ 7.42-6.65 ppm (multiplet due to 3H aromatic protons), δ 4.19 ppm (singlet due to NH proton), δ 4.02-3.77 ppm (triplet due to CH_2 protons at C_3), δ 3.40-3.23 ppm (triplet due to CH_2 protons at C_2). Anal. data for C_8H_8NSCl: Calcd. C 51.75, H 4.34, N 7.54; Found C 51.59, H 4.36, N 7.58

Compound 6. 7-Chloro-4-(N-butylamido)-2, 3-dihydro-1,4-benzothiazine

IR: 3270 cm^{-1} (N-H-stretching), 1670 cm^{-1} (co stretching), 730 (C- Cl stretching)

^1H NMR ($CDCl_3$):

δ 7.57-6.49 ppm (multiplet due to 3H aromatic protons), δ 5.13 ppm (singlet due to NH proton), δ 4.44-4.09 ppm (triplet due to CH_2 protons at C_3), δ 3.45-3.10 ppm (triplet due to CH_2 protons at C_2), δ 2.90-2.75 ppm (triplet due to CH_2 protons at $C_{1'}$ of butyl group), δ 1.71-1.27 ppm (multiplet due to CH_2 CH_2 protons at $C_{2'}$ and $C_{3'}$ of butyl group), δ 1.11-0.94 ppm (triplet due to CH_3 protons at $C_{4'}$ of butyl group). Anal. data for $C_{13}H_{17}N_2SOCl$: Calcd. C 54.82, H 6.01, N 9.84 Found C 54.97, H 5.98, N 9.80

Compound 7. 7-Chloro-4-(N-butyl-N-nitrosoamido)-2, 3-dihydro-1, 4-benzothiazine

IR: 1580 cm^{-1} (co stretching), 720 (C- Cl stretching)

^1H NMR ($CDCl_3$):

δ 7.76-6.75 ppm (multiplet due to 3H aromatic protons), δ 4.09-3.86 ppm (triplet due to CH_2 protons at C_3), δ 3.52-3.33 ppm (triplet due to CH_2 protons at C_2), δ 2.95-2.79 ppm (triplet due to CH_2 protons at $C_{1'}$ of butyl group), δ 2.30-2.17 ppm (multiplet due to CH_2 CH_2 protons at $C_{2'}$ and $C_{3'}$ of butyl group), δ 1.30-1.00 ppm (triplet due to CH_3 protons at $C_{4'}$ of butyl group). Anal. data for $C_{13}H_{16}N_3SO_2Cl$: Calcd. C 49.76, H 5.14; N 13.39 Found C 49.99, H 5.11 N 13.46

The purity of the synthesized compounds was checked by thin layer chromatography (TLC). The infrared spectra were recorded at a Perkin-Elmer spectrophotometer model 577. The ^1H NMR spectra were recorded at a 90 MHz Jeol FX 90 Q NMR in $CDCl_3$ containing TMS as internal standard.

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