Research Article

One pot multicomponent synthesis and biological screening of novel Chloroacetyl amino benzothiazoles

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Abstract

Objective: A Literature survey shows that benzothiazole and its derivatives possess different microbial activities, which of most potent activity is anti-bacterial activity. The objectives of the present work are to synthesize certain benzothiazole derivatives and study their antibacterial activity in particular. **Materials and methods:** A mixture of 4-substituted aniline, potassium thiocyanate and bromine 5^0C in glacial acetic acid which on reflux with chloroacetyl chloride in benzene at 70^0C yields 2-chloroacetyl amino-6-substituted benzothiazole. The synthesized compounds were characterized by elemental analysis and spectral data. **Results and conclusion:** As expected substituted benzothiazoles exhibited antimicrobial activity. 2-chloroacetyl amino-6-substituted benzothiazole moieties independently showed a broad spectrum of antibacterial activity against Gram positive and Gram negative bacteria.

Keywords: 4-substituted aniline, potassium thiocyanate, glacial acetic acid, chloroacetyl chloride

Introduction

Multicomponent reactions constitute an especially attractive, synthetic strategy and they provide easy and rapid access to large libraries of organic compounds with different substitution patterns. The "ideal synthesis" should lead to the desired product. The multicomponent reaction is useful is due to optimized time, cost, simplicity of performance, safety, overall yield and environmental acceptability. In multistep syntheses (Hantzsch, 1890; Biginelli, 1891; Robinson, 1917; Passerini, 1921; Bergs, 1929) the temporal and preparative complexity increases in proportion to the number of steps. It is reflected in many isolation and purification operations, such as crystallization, extraction, distillation, or chromatography.

In spite of the significant useful attributes of MCRs for modern organic chemistry and their suitability for building up large compound libraries these reactions were of limited interest in the past fifty years. However, in the last decade, with introduction of high-throughput biological screening, the importance of MCRs for drug discovery has been recognized and considerable efforts from both academic and industrial researchers have been focused especially on the design and the development of multicomponent procedures for the generation of libraries of heterocyclic compounds. This growing interest is stimulated by the significant therapeutic potential that is associated with many heterocycles. Furthermore, the utility of rigid well defined structures of heterocycles was demonstrated in many detailed structure activity relationship (SAR) studies. Besides the multistep, sequential synthesis of a target molecule, the desired product can also be obtained in one-pot reactions of three or more starting compounds, the multicomponent reactions (MCRs). Here the starting materials do not react simultaneously in one step, but rather in a sequence of elementary steps according to a program. Reactions with an irreversible step, which drives the preceding equilibrium to the product side, are especially favorable. Many products can be synthesized from only a few starting substances. As MCRs, being one-pot reactions, are practically single-step conversions, they are easier to carry out than multistep synthesis.

Benzothiazoles are very important class of compounds that occur widely as biologically and pharmacologically active natural products, as well as marketed drugs (Chau et al., 2007) Accordingly, the development of efficient and general synthetic methodology for Benzothiazole is a meaningful research challenge having great potential for practical applications in the pharmaceutical industry.

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Substituted benzothiazole is an important class of heterocyclic compounds that exhibits a wide range of biological properties such as inhibitors of stearoyl-coenzyme desaturase (Black et al., 2006), antitumor (Bradshaw et al., 1998; Kashiyama et al., 1999; Hutchinson et al., 2001), used as antimicrobial (Palmer et al., 1971), also used as LTD_4 receptor antagonist (Lau et al., 1995), used as new drugs such as the orexin receptor antagonist (Bergman et al., 2006) and Gram-positive selective antibacterials (Ali et al., 2001). Pyrimido [2,1-*b*] benzothiazole and its 8-substitued derivatives were found to have antiviral activity. Benzothiazole derivatives are very important group of heterocyclic system which plays a vital role in organic and bioorganic chemistry. They have potent antitumor activity and pharmaceutical utilities (Chen and Chen, 2004; Tale, 2002; Mathis et al., 2003; Jackson et al., 2000).

Materials and methods

General procedure for synthesis of 2-chloroacetyl amino-6-substituted benzothiazoles (a-d)

A mixture of 1 mole of 4-substituted aniline, 1 mole of potassium thiocyanate and glacial acetic acid (10 ml) cooled to 5^0C. The reaction mixture was placed in freezing mixture of ice and salt and mechanically stirred, while 1.1 ml of bromine in 4.0 ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature does not rise beyond 0^0C. After all the bromine has been added the solution was stirred for an additional two hours at 0^0C. Then add 5 ml solution of chloroacetyl chloride in benzene which on reflux at 70^0C on a water bath for 90 min. It was then allowed to stand overnight and precipitate is settled at the bottom. Filter the product and wash with water. The combined filtrate was cooled and neutralized carefully with ammonia solution (pH 6.0) and then a dark yellow precipitate was separated and was collected. The product was recrystallized twice with benzene gave product known as 2-chloroacetyl amino-6-substituted benzothiazoles.

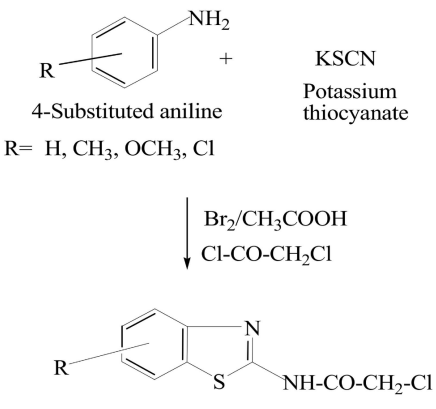

Figure 1. Different steps for synthesis of 2-chloroacetyl amino-6-substituted benzothiazoles (a-d)

(i) synthesis of 2-chloroacetyl amino benzothiazole (a)

A mixture of 1 mole of aniline, 1 mole of potassium thiocyanate and glacial acetic acid (10 ml) cooled to 5^0C. The reaction mixture was placed in freezing mixture of ice and salt and mechanically stirred, while 1.1 ml of bromine in 4.0 ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature does not rise beyond 0^0C. After all the bromine has been added the solution was stirred for an additional two hours at 0^0C. Then add 5 ml solution of chloroacetyl chloride in benzene which on reflux at 70^0C on a water bath for 90 min. It was then allowed to stand overnight and precipitate is settled at the bottom. Filter the product and wash with water. The combined filtrate was cooled and neutralized carefully with ammonia solution (pH 6.0) and then a dark yellow precipitate was separated and was collected. The product was recrystallized twice with benzene gave product known as 2-chloroacetyl amino benzothiazole.

(ii) Synthesis of 2-chloroacetyl amino-6-methyl benzothiazole (b)

A mixture of 1 mole of 4-methyl aniline, 1 mole of potassium thiocyanate and glacial acetic acid (10 ml) cooled to 5^0C. The reaction mixture was placed in freezing mixture of ice and salt and mechanically stirred, while 1.1 ml of bromine in 4.0 ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature does not rise beyond 0^0C. After all the bromine has been added the solution was stirred for an additional two hours at 0^0C. Then add 5 ml solution of chloroacetyl chloride in benzene which on reflux at 70^0C on a water bath for 90 min. It was then allowed to stand overnight and precipitate is settled at the bottom. Filter the product and wash with water. The combined filtrate was cooled and neutralized carefully with ammonia solution (pH 6.0) and then a dark yellow precipitate was separated and was collected. The product was recrystallized twice with benzene gave product known as 2-chloroacetyl amino-6-methyl benzothiazole.

(iii) Synthesis of 2-chloroacetyl amino-6-methoxy benzothiazole (c)

A mixture of 1 mole of 4-methoxy aniline, 1 mole of potassium thiocyanate and glacial acetic acid (10 ml) cooled to 5^0C. The reaction mixture was placed in freezing mixture of ice and salt and mechanically stirred, while 1.1 ml of bromine in 4.0 ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature does not rise beyond 0^0C. After all the bromine has been added the solution was stirred for an additional two hours at 0^0C. Then add 5 ml solution of chloroacetyl chloride in benzene which on reflux at 70^0C on a water bath for 90 min.

It was then allowed to stand overnight and precipitate is settled at the bottom. Filter the product and wash with water. The combined filtrate was cooled and neutralized carefully with ammonia solution (pH 6.0) and then a dark yellow precipitate was separated and was collected. The product was recrystallized twice with benzene gave product known as 2-chloroacetyl amino-6-methoxy benzothiazole.

(iv) Synthesis of 2-chloroacetyl amino-6-chloro benzothiazole (d)

A mixture of 1 mole of 4-chloro aniline, 1 mole of potassium thiocyanate and glacial acetic acid (10 ml) cooled to 5^0C. The reaction mixture was placed in freezing mixture of ice and salt and mechanically stirred, while 1.1 ml of bromine in 4.0 ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature does not rise beyond 0^0C. After all the bromine has been added the solution was stirred for an additional two hours at 0^0C. Then add 5 ml solution of chloroacetyl chloride in benzene which on reflux at 70^0C on a water bath for 90 min. It was then allowed to stand overnight and precipitate is settled at the bottom. Filter the product and wash with water. The combined filtrate was cooled and neutralized carefully with ammonia solution (pH 6.0) and then a dark yellow precipitate was separated and was collected. The product was recrystallized twice with benzene gave product known as 2-chloroacetyl amino-6-chloro benzothiazole.

Characterization of synthesized compounds

(a) 2-chloroacetyl amino benzothiazole

Yield = 67 %, Melting Point : 251^0C, IR: (KBr / cm^{-1}): 3218 (-NH), 3110 (Ar-H), 1720 (-C≡ O), 1620 (C=N), ^{1}H-NMR: (DMSO) **:** 8.23 (d 2H Ar-H), 7.55 (d 2H Ar-H), 8.00 (s 1H -NH), 4.25 (s 2H $–CH_2$), MS: (m/z : RA %): = 226 (M+1), Elemental analysis : $C_9H_7ClN_2OS$, Calculated: (%) C 47.69, H 3.11, Cl 15.64, N 12.36, O 7.06, S 14.15 Found (%): C 47.61, H 3.07, Cl 15.60, N 12.32, O 7.03, S 14.11.

(b) 2-chloroacetyl amino-6-methyl benzothiazole

Yield = 54 %, Melting Point : 219 ^{0}C, IR: (KBr / cm^{-1}): 3211 (-NH), 3112 (Ar-H), 1722 (-C≡ O), 1615 (C=N), ^{1}H-NMR: (DMSO) **:** 8.11 (d 1H Ar-H), 7.52 (s 1H Ar-H), 7.35 (d 1H Ar-H), 8.01 (s 1H -NH), 4.27 (s 2H $–CH_2$), 2.33 (s 3H $–CH_3$), MS: (m/z : RA %): = 241 (M+1), Elemental analysis : $C_{10}H_9ClN_2OS$, Calculated: (%) C 49.00, H 3.77, Cl 14.73, N 11.64, O 6.65, S 13.32 Found (%): C 48.92, H 3.71, Cl 14.70, N 11.62, O 6.61, S 13.30.

(c) **2-chloroacetyl amino-6-methoxy benzothiazole**

Yield = 61 %, Melting Point : 189 ^{0}C, IR: (KBr / cm^{-1}): 3205 (-NH), 3108 (Ar-H), 1717 (-C≡ O), 1610 (C=N), ^{1}H-NMR: (DMSO) **:** 8.12 (d 1H Ar-H), 7.62 (s 1H Ar-H), 7.05 (d 1H Ar-H), 7.95 (s 1H -NH), 4.26 (s 2H $–CH_2$), 3.73 (s 3H $–CH_3$), MS: (m/z : RA %): = 257 (M+1), Elemental analysis : $C_{10}H_9ClN_2O_2S$, Calculated: (%) C 46.79, H 3.53, Cl 13.81, N 10.91, O 12.47, S 12.49 Found (%): C 46.77, H 3.50, Cl 13.75, N 10.88, O 12.45, S 12.47.

(d) 2-chloroacetyl amino-6-chloro benzothiazole

Yield = 71 %, Melting Point : 207 ^{0}C, IR: (KBr / cm^{-1}): 3200 (-NH), 3105 (Ar-H), 1715 (-C≡O), 1608 (C=N), ^{1}H-NMR: (DMSO) **:** 8.17 (d 1H Ar-H), 8.13 (s 1H Ar-H), 7.55 (d 1H Ar-H), 7.99 (s 1H -NH), 4.27 (s 2H $–CH_2$), MS: (m/z : RA %): = 262 (M+1), Elemental analysis : $C_9H_6Cl_2N_2OS$, Calculated: (%) C 41.40, H 2.32, Cl 27.15, N 10.73, O 6.13, S 12.28 Found (%):C 41.36, H 2.30, Cl 27.11, N 10.70, O 6.11, S 12.25.

Biological screening of novel chloroacetyl amino substituted benzothiazoles

All newly synthesized novel chloroacetyl amino substituted benzothiazoles (a-d) were evaluated in-vitro for antibacterial activity against gram positive and gram negative bacterial strain such as *Bacillus subtilis, Bacillus Megatenium*, *Escherichia coli* and *Pseudomonas aureginosa* atconcentration 100µ/ml by disc diffusion method[24] by using DMSO as solvent control and nutrient agar was employed as culture media. After 24h of incubation at 37^0C, the zone of inhibition was measured in mm. The activity was compared with known antibiotic Streptomycin and the data was represented in table 1.

Table 1. Antibacterial activity of chloroacetyl amino substituted benzothiazoles (a-d)

Sample code	*Zone of inhibition (diameter in mm)			
	B. subtilis	***B. Megatenium***	***E. coli***	***P. aureginosa***
	100µ/ml	100µ/ml	100µ/ml	100µ/ml
a	23	20	07	10
b	22	27	16	12
c	14	17	19	21
d	21	23	17	20
Streptomycin	31	35	28	27
DMSO	-	-	-	-

*Each value is an average of three independent determinations ± Standard deviation. **Note:** '-' denotes no activity, 8-12 mm poor activity, 13-17 mm moderate activity,18-20 mm and above good activity.

Results and discussion

As expected novel chloroacetyl amino substituted benzothiazoles exhibited antimicrobial activity, some are equipotent to that of standard employed for comparison. Therefore a detailed study of toxicity is necessary. The objectives of the present work are to synthesize novel chloroacetyl amino substituted benzothiazole derivatives and study their antibacterial activity. Thus an attempt has

been made in this direction. There is no such a thing as completely safe drug. Drugs are powerful tools which alter physiological processes for the better or for the worse. A society which wishes to benefit from them will not achieve all the benefits are for the biological testing do not always turn out as potential new drugs, but may be intended to serve as models for evaluation of hypothesis.

The screening for antibacterial activity of newly synthesized compound 2-chloroacetyl amino-6-substituted benzothiazoles (a-d) have been studied against gram positive and gram negative bacterial strain such as Bacillus subtilis, Bacillus Megatenium**,** Escherichia coli and Pseudomonas aureginosa bacteria by well diffusion method.

Compound a, b and d exhibited the zone of inhibition in between 20 mm to 23 mm in diameter shows good antibacterial activity against gram positive Bacillus subtilis and Bacillus Megatenium bacteria. Compounds 'c' exhibited the zone of inhibition in between 14 mm to 17 mm in diameter shows moderate antibacterial activity against gram positive Bacillus subtilis and Bacillus Megatenium bacteria. Compound 'c' and 'd' exhibited the zone of inhibition in between 17 mm to 20 mm in diameter shows good antibacterial activity against gram negative Escherichia coli and Pseudomonas aureginosa bacteria. Compound 'b' exhibited the zone of inhibition in between 12 mm to 16 mm in diameter shows moderate antibacterial activity and compound 'a' exhibited the zone of inhibition in between 07 mm to 10 mm in diameter shows poor antibacterial activity against gram negative Escherichia coli and Pseudomonas aureginosa bacteria.

Conclusion

2-chloroacetyl amino-6-substituted benzothiazole moieties independently showed a broad spectrum of antibacterial activity against Gram positive and Gram negative bacteria. 2-chloroacetyl amino-6-substituted benzothiazoles are responsible for antibacterial activity, but it is interesting to note that benzothiazole moieties when fused with other moieties showed a broad spectrum antibacterial activity. Hence in search of new generation of antibiotics it may be worthwhile to explore the possibility in this area by fusing different moieties and increase potency.

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Conflicts of interest

The author declares no financial conflicts of interest.

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