



Research Article

ANTIBACTERIAL ACTIVITY OF NOVEL HYDROXY SUBSTITUTED BENZOTHAIAZOLE DERIVATIVES AGAINST *STREPTOCOCCUS PYOGENES*

Akhilesh Gupta *

Kunwar Haribansh Singh College of Pharmacy, Jaunpur (UP), India

*Corresponding Author Email: 81.akgupta@gmail.com

Article Received on: 19/06/18 Approved for publication: 30/06/18

DOI: 10.7897/2230-8407.096118

ABSTRACT

Synthesis and screening of benzothiazole derivatives have great importance in heterocyclic chemistry because of its potent and significant biological activities against *Streptococcus (S) pyogenes* especially hydroxy substitution at benzothiazole. Hydroxy-substituted benzothiazole derivatives were synthesized by reaction of 4-amino-2-chlorophenol with potassium thiocyanate under temperature control and presence of bromine in glacial acetic acid and ammonia. Hydroxy-substituted nitrobenzamides then synthesized by condensation of 2-amino-4-chlorobenzothiazol-5-ol with 2(3or4)-nitrobenzoylchloride acid in presence of dry pyridine and acetone. Finally, newly synthesized derivatives (A-01 to A-09) were synthesized through replacing of chlorine of nitrobenzamide by reaction with 2-nitroaniline, 3-nitroaniline, and 4-nitroaniline in presence of DMF. Analytical characterization was performed by TLC, melting point, IR and NMR spectra. Antibacterial activity was performed against *S. pyogenes* by cup plate method (diffusion technique) using procaine penicillin as standard. Compound A-03, A-04 and A-08 showed potent antibacterial activity against *S. pyogenes* at both concentrations 50µg/ml and 100µg/ml as compared to standard while the rest of compounds showed moderate to negligible activity when further assessed to determine MIC by broth dilution method.

KEYWORDS: Hydroxy-benzothiazole, Benzothiazole, Antibacterial, 2-substituted benzothiazole, Benzothiazole cyclization, *Streptococcus pyogenes*

INTRODUCTION

Benzothiazole is a therapeutically important privileged bicyclic ring system contains sulphur and nitrogen as a heteroatom. Synthesis and screening of benzothiazole derivatives have great importance in heterocyclic chemistry because of its potent and significant biological activities. Substitution at C-2 of benzothiazole nucleus has emerged in its usage as a core structure in the diversified therapeutically applications¹⁻⁵. As per reported biological activities of benzothiazole derivatives it was found that change of the structure of substituent group at benzothiazole nucleus commonly results in the change of its bioactivities. Commonly change of substitution at C-2 benzothiazole nucleus especially with aryl-nitro has already been proven its therapeutic importance. Till date, various biological activities for benzothiazole derivatives have been reported as antitumor, antitubercular, antimalarial, anticonvulsant, anthelmintic, analgesic, anti-inflammatory, antibacterial and antifungal, a topical carbonic anhydrase inhibitor and an antihypoxic⁶⁻⁹. 2-substituted benzothiazole derivatives were first discovered in 1887 by A. W. Hofmann as simple cyclization mechanism and number of the synthetic scheme has been reported. The most common and classical method was reported as direct method that involved condensation of an ortho-amino thiophenol with a substituted aromatic aldehyde, carboxylic acid, acyl chloride or nitrile to synthesize C-2 substituted benzothiazoles, but it was found that this method is not appropriate for majority of substituted C-2 aryl benzothiazoles because the main difficulty encountered in synthesis of the readily oxidisable 2-amino thiophenols bearing substituent groups. For above said reason some other methods were reported and extensively used in the laboratories that based on the use of the potassium ferricyanide radical cyclization of thiobenzanilides¹⁰. This method was named

as Jacobsen cyclization and popularized because it produced only one product. As per reported method, it involved cyclization onto either carbon atom ortho to the anilido nitrogen. Because of selective product synthesis, the Jacobsen cyclization was considered as a highly effective strategy for benzothiazole synthesis e.g. for the synthesis of substituted benzothiazoles, radical cyclization of the 3-fluoro- or 3,4-difluoro-substituted thiobenzanilides¹¹⁻¹⁷. Since severe infections caused by the Lancefield group especially *S. pyogenes* are relatively uncommon, affecting around 3 per 100,000 of the population per annum in developed countries ranging from the ubiquitous pharyngitis to rarer life-threatening in terms of clinical spectra and severity. The case fatality is high relative to many other infections, around 7-23%. The rapidity with which patients can deteriorate bestows further notoriety to this pathogen, inducing disquiet among frontline medical staff faced with a differential diagnosis, and fear amongst the public at large. Although attributable mortality is higher among the elderly and those with impaired immune systems, deaths among the young and previously healthy are not uncommon. In 1994 the major events for severe *S. pyogenes* disease were detected in Gloucestershire, in the South West of England¹⁸⁻²¹. Like other members of the family *Streptococcaceae*, *streptococci* are Gram-positive facultative anaerobic organisms which occur in chains or in pairs. Theodor Billroth proposed the name for *Streptococcus* through the identification of these organisms in the patients with erysipelas and wound infections. *Streptococci* were first classified at the turn of the 20th Century according to their differential capacity to induce haemolysis on blood agar. Pioneering work by Rebecca Lancefield during the 1930s proposed a serological classification scheme based on group-specific polysaccharides. She further subdivided group A *streptococci* according to the M protein found on the cell wall, an

important virulence factor against which protective antibodies are formed. Carriage rates vary according to geographical location, climatic factors, season and age. Estimates of pharyngeal carriage range from 12-23% in school-aged children²². Different M-types are known to favour mucosal versus cutaneous sites, the latter constituting the higher-numbered types in the reflection of their more recent identification. There is some evidence that some serotypes have more pathogenic potential than others. Transmission of *S. pyogenes* is usually through direct contact with droplets of saliva or nasal secretions from carriers or persons with clinical infection, or through skin contact, especially contact with infected lesions. Seminal work carried out at the Warren Air Force base in Wyoming (USA) found transmission rates to be higher in symptomatic than asymptomatic individuals, from individuals carrying the organism in their nose than the throat, and from those heavily colonized. Transmission rates have also been found to be increased by crowding. The length of incubation is usually fairly short, usually 1-3 days. The period of communicability is typically 10-21 days in untreated individuals with uncomplicated infection. This is significantly reduced once antibiotic treatment has commenced, with less than 20% of children in one study found to have a positive throat swab 24 hours after commencement of treatment. Staphylococcal infection presents most commonly in the skin and soft tissues²⁰⁻²³. These infections cause over ten million outpatient visits and nearly a half-million hospital admissions per year in the world²⁴⁻³¹. The present work concern with the synthesis of hydroxy and aryl-nitro substituted benzothiazole derivatives followed by the antibacterial activity for structure-activity relationship against *S. pyogenes*.

MATERIALS AND METHODS

All chemicals were purchased from Alfa Aesar and solvents were used without further purification. Analytical thin-layer chromatography (TLC) was performed with E. Merck silica gel GF254 glass plates and detection performed by exposing them to iodine vapours. Melting points (MP) were determined with Shimadzu DS-50 thermal analyzer. The FT-IR spectra were obtained using KBr pellets on Shimadzu spectrometer Japan (8400S). ¹HNMR Bruker (AM 400), Japan was used using CDCl₃ as a solvent and tetramethoxysilane (TMS) as an internal standard.

Synthesis of substituted benzothiazole (Compound Code 1-AB)

Synthesis of C-6 hydroxy benzothiazole nucleus was achieved by adding 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of 4-amino-2-chlorophenol into 20 ml cooled glacial acetic acid in such a way that the temperature not exceeded above room temperature. Freezing mixture of ice and salt was used to control the temperature of reaction with continuous mechanical stirring. Again temperature control was maintained during the addition of a solution of 1.6ml of bromine in 6ml of glacial acetic acid using dropping funnel. The time of addition of bromine also considered to take around 105 minute to control temperature. During the addition of bromine, temperature was controlled to never rise beyond the room. As the addition of bromine was completed the solution stirred for 2 hours but below room temperature. After that solution was again stirred at room temperature for 10 hours and allowed to stand overnight to get precipitate followed by heating at 85°C on a steam bath after addition of 6ml water and filtered hot (Filtrate-01). In the resulting precipitate 10ml of glacial acetic acid was added and heated with at 85°C and filtered hot (Filtrate-02). Finally, both filtrate combined and cooled at room temperature followed by neutralization with concentrated ammonia solution to pH-6 to get precipitate. The resulting

product treated with animal charcoal and recrystallized from benzene, ethanol of (1:1) to yield substituted benzothiazole.

Synthesis of nitrobenzamide (Compound code 2-AB, 3-AB, and 4-AB)

5.36g (0.026mol) of 2-(3 or 4)-nitrobenzoylchloride was dissolved in dry acetone. Product 1-AB separately dissolved in dry pyridine and added drop wise into the solution of 2-(3 or 4)-nitrobenzoylchloride with continuous stirring at room temperature. After complete addition stirring was continued for another 30 minutes then transferred into 200 ml ice cold water. Finally recrystallized with ethanol to get intermediate nitrobenzamide compound 2-AB, 3-AB and 4-AB.

Synthesis of compound A-01 to A-09

0.008 mol of 2 (3 or 4) nitro-substituted aniline was refluxed with 2.7g (0.0075 mol) of compound 2-AB, 3-AB and 4-AB separately for 2hrs in the presence of DMF. After 2 hrs reflux, mixture cooled at room temperature and poured into crushed ice. The solid was separated, dried and recrystallized with super dry alcohol to get novel benzothiazole derivatives A-01 to A-09 (Figure 1).

General synthesis of N-{6-hydroxy-7-[(2-nitrophenyl)-amino] 1, 3-benzothiazole-2-yl}-2-nitrobenzamides (Comp. code A-01)

Percentage yield-62, MP-264-269°C, Rf value-0.45, IR Range-1469cm⁻¹Ar C=C, 1648cm⁻¹C=O, 1255cm⁻¹C-S, 1540cm⁻¹C-NO₂, 3002cm⁻¹C-CH₃. δ 4.66, (s, 1H, NH), δ 5.21(s, 1H, OH), δ 7.33-7.80 (m, 10H, Ar-H), δ 8.80 (s, 1H, C-NH)

General synthesis of N-{6-hydroxy-7-[(3-nitrophenyl)-amino]1,3-benzothiazole-2-yl}- 2-nitrobenzamides (Comp. code A-02)

Percentage yield- 68, MP-274-278°C, Rf value-0.39, IR Range-1454cm⁻¹Ar C=C, 1640cm⁻¹C=O, 1257cm⁻¹C-S, 1575cm⁻¹C-NO₂. δ 4.23, (s, 1H, NH), δ 5.26(s, 1H, OH), δ 7.29-7.80 (m, 10H, Ar-H), δ 9.15 (s, 1H, C-NH)

General synthesis of N-{6-hydroxy-7-[(4-nitrophenyl)-amino]1,3-benzothiazole-2-yl}- 2-nitrobenzamides (Comp. code A-03)

Percentage yield-71, MP-260-265°C, Rf value-0.33, IR Range-1478cm⁻¹Ar C=C, 1668cm⁻¹C=O, 1221cm⁻¹C-S, 1563cm⁻¹C-NO₂. δ 4.50, (s, 1H, NH), δ 5.29(s, 1H, OH), δ 7.20-7.69 (m, 10H, Ar-H), δ 8.80 (s, 1H, C-NH)

General synthesis of N-{6-hydroxy-7-[(2-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code A-04)

Percentage yield-65, MP-258-264°C, Rf value-0.46, IR Range-1425cm⁻¹Ar C=C, 1653cm⁻¹C=O, 1241cm⁻¹C-S, 1560cm⁻¹C-NO₂. δ 4.66, (s, 1H, NH), δ 5.25(s, 1H, OH), δ 7.27-7.71 (m, 10H, Ar-H), δ 8.91 (s, 1H, C-NH)

General synthesis of N-{6-hydroxy-7-[(3-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code A-05)

Percentage yield-78, MP-269-273°C, Rf value-0.44, IR Range-1422cm⁻¹Ar C=C, 1665cm⁻¹C=O, 1240cm⁻¹C-S, 1551cm⁻¹C-NO₂. δ 4.53, (s, 1H, NH), δ 5.18(s, 1H, OH), δ 7.28-7.78 (m, 10H, Ar-H), δ 8.92 (s, 1H, C-NH)

General synthesis of N-{6-hydroxy-7-[4-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-3-nitrobenzamides (Comp. code A-06)

Percentage yield-76, MP-263-268°C, Rf value-0.48, IR Range-1433cm⁻¹Ar C=C, 1619cm⁻¹C=O, 1234cm⁻¹C-S, 1539cm⁻¹C-NO₂. δ 4.24, (s, 1H, NH), δ 5.34(s, 1H, OH), δ 7.12-7.77 (m, 10H, Ar-H), δ 9.09 (s, 1H, C-NH)

General synthesis of N-{6-hydroxy-7-[2-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code A-07)

Percentage yield-69, MP-275-280°C, Rf value-0.50, IR Range-1455cm⁻¹Ar C=C, 1612cm⁻¹C=O, 1234cm⁻¹C-S, 1533cm⁻¹C-NO₂. δ 4.59, (s, 1H, NH), δ 5.30(s, 1H, OH), δ 7.15-7.90 (m, 10H, Ar-H), δ 8.99 (s, 1H, C-NH)

General synthesis of N-{6-hydroxy-7-[2-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code A-08)

Percentage yield-61, MP-262-265°C, Rf value-0.48, IR Range-1417cm⁻¹Ar C=C, 1662cm⁻¹C=O, 1212cm⁻¹C-S, 1512cm⁻¹C-NO₂. δ 4.60, (s, 1H, NH), δ 5.33(s, 1H, OH), δ 7.10-7.68 (m, 10H, Ar-H), δ 8.89 (s, 1H, C-NH)

General synthesis of N-{6-hydroxy-7-[4-nitrophenyl)-amino]1,3-benzothiazole-2-yl}-4-nitrobenzamides (Comp. code A-09)

Percentage yield-73, MP-277-283°C, Rf value-0.54, IR Range-1426cm⁻¹Ar C=C, 1630cm⁻¹C=O, 1238cm⁻¹C-S, 1537cm⁻¹C-NO₂. δ 4.62, (s, 1H, NH), δ 5.21(s, 1H, OH), δ 7.36-7.93 (m, 10H, Ar-H), δ 9.15 (s, 1H, C-NH)

Antibacterial activity against *S. pyogenes* using procaine penicillin as standard

The standard drug and synthesized compounds were dissolved in minimum quantity of dihydroxy formamide (DMF) and adjusted and made up the volume with distilled water to get 50µg/ml and 100µg/ml concentrations. The antibacterial activity was performed by cup plate method (diffusion technique). The fresh culture of bacteria was obtained by inoculating bacteria into peptone water liquid media and incubated at 37 ± 2°C for 18 – 24 hours. This culture mixed with nutrient agar media (20%) and poured into petridishes by following aseptic techniques. After solidification of the media five bores were made at equal distance by using sterile steel cork borer (8 mm diameter). Into these cups different concentrations of standard drug and synthesized compounds were introduced. Dihydroxy formamide was used as a control. After introduction of standard drug and synthesized compounds, the plates were placed in a refrigerator at 8°C -10°C for proper diffusion of drugs into the media. After two hours of cold incubation, the petriplates are transferred to incubator and maintained at 37±2°C for 18-24 hours. After the incubation period, the petriplates were observed for zone of inhibition by using vernier scale. The results evaluated by comparing the zone of inhibition shown by the synthesized compounds with standard drug. The results are the mean value of zone of inhibition measured in millimeter of two sets.

Minimum inhibitory concentration (MIC) by broth dilution method

Nutrient broths (double strength) was prepared in test tubes and labeled them. In first test tube (UT), inoculum is not added which is used for checking the sterility of medium and as a negative control. Other all test tubes, inoculums (three to four drops) is added to reach the final concentration of micro-organisms is 10⁶ cells/ml in all test tubes, test antimicrobial compound is added ranging from 0.5 to 5 ml except uninoculated (negative control) and control (positive) tube. The positive control tube is used to check the suitability of the medium for growth of the test microorganism and the viability of the inoculum. Adjust the final volume (10 ml) in all test tubes by using sterile water. All test tubes are properly shaken and then incubated at 37°C for two days.

RESULT AND DISCUSSION

Hydroxy substituted benzothiazole nucleus while 2-(3 or 4)-arylnitro considered as rotating substitution at C-2 and C-4 position of benzothiazole nucleus derivatives were synthesized as per synthetic scheme shown in Figure 1. The novel derivatives (A-01 to A-09) evaluated for antibacterial activity against *S. pyogenes*. In the present work nitro group consider as rotating basis on ortho, meta and para position. The reason behind considering nitro group as substituent is the bacteria rarely acquire resistance. TLC, melting point, IR and ¹HNMR were used for analytical characterization. In the TLC, the distance traveled by compound A-01 to A-09 was found to be different from that of the starting compound that proved synthesized compounds were different from parent one, even during TLC performance every time single spot was obtained, hence it also reveals that synthesized compounds were free from impurity as well as reaction was completed. Structure elucidation by IR spectroscopy frequency range for Ar C=C, C=O, C-S, C-NO₂ was considered. In case of structure elucidation of by ¹HNMR sharp characteristic signal at, 1H-NH, 1H-OH, 10H- Ar-H, 1H-CONH was observed in all the synthesized compounds. Antibacterial activity performed at two concentration 50µg/ml and 100µg/ml using procaine penicillin as a standard drug against *S. pyogenes*. Compound A-03, A-04 and A-08 showed potent antibacterial activity against *S. pyogenes* at both concentrations 50µg/ml and 100µg/ml as compared to standard. All the synthesized compounds exhibited significant, moderate even negligible activity at two different concentrations (50µg/ml and 100µg/ml) when zone of inhibition determined using procaine penicillin as a standard drug. The result of zone of inhibition at both concentration 50µg/ml and 100µg/ml has been depicted in Tables 1, Figure 2 for 50µg/ml and Figure 3 for 100µg/ml. Further, the compounds were assessed to determine MIC by broth dilution method in order to further evaluate and validate result zone of inhibition. The result of MIC determination is illustrated in Table 2. Present study suggested that the structural substitution of synthesized compounds may have better impact on changing the efficacy of antibacterial activity when further screened for MIC. The result of present study showed that all the compounds displayed a varied degree of MIC ranging from 20.61 ± 0.29 to 10.35 ± 0.14 at 50µg/ml and 32.45 ± 0.75 to 13.62 ± 0.25 at 100µg/ml. The result of MIC obtained after the entire study shown in Figure 4 for 50µg/ml and Figure 5 for 100µg/ml. Among all the synthesized compounds, the compound A-03, A-04 and A-08 exhibited excellent antibacterial activity. Nevertheless, the remaining compounds showed negligible antibacterial activity against all the tested strains. The comparative study of result obtained for zone of inhibition described in Figure 6 while result of MIC depicted in Figure 7.

Table 1: Antibacterial activity data of synthesized compounds against *Streptococcus pyogenes*

Compound Code	Zone of Inhibition (mm)*	
	<i>Streptococcus pyogenes</i>	
	50 µg/ml	100 µg/ml
Procaine penicillin (PP)	22	34
A-01	10	14
A -02	10	16
A -03	20	33
A -04	20	31
A -05	12	19
A -06	14	24
A -07	14	21
A -08	21	33
A -09	10	18
Control	0	0

*Each value is the mean of three replicates

Table 2: MIC value of synthesized compounds against *Streptococcus pyogenes*

Compound Code	Minimum inhibitory concentration (MIC) µg/ml ± SD*	
	<i>Streptococcus pyogenes</i>	
	50 µg/ml	100 µg/ml
Procaine penicillin (PP)	21.11 ± 0.62	32.08 ± 0.22
A-01	10.38 ± 0.15	13.62 ± 0.25
A -02	10.66 ± 0.45	12.20 ± 0.24
A -03	20.61 ± 0.29	32.45 ± 0.75
A -04	19.22 ± 0.09	30.09 ± 0.42
A -05	11.21 ± 0.26	17.47 ± 0.25
A -06	12.21 ± 0.08	21.64 ± 0.78
A -07	13.46 ± 0.64	17.32 ± 0.08
A -08	20.04 ± 0.87	30.54 ± 0.26
A -09	10.35 ± 0.14	17.73 ± 0.60
Control	0	0

*Each value is the mean of three replicates

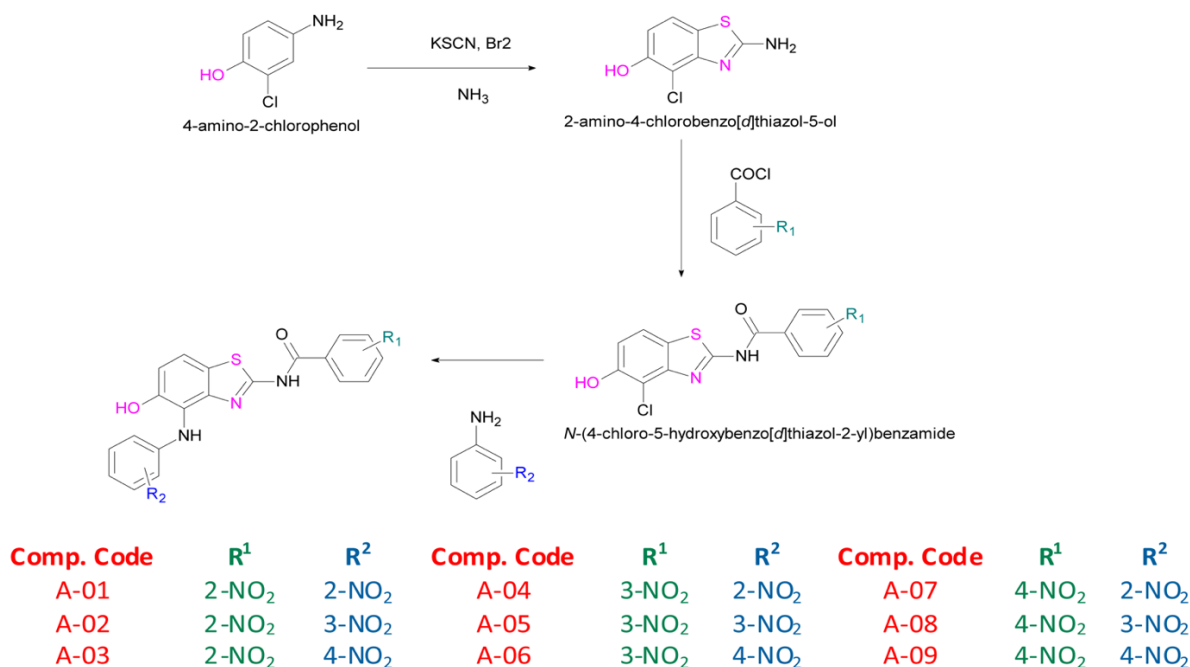


Figure 1: Synthetic scheme for novel hydroxy substituted benzothiazole derivatives (A-01 to A-09)

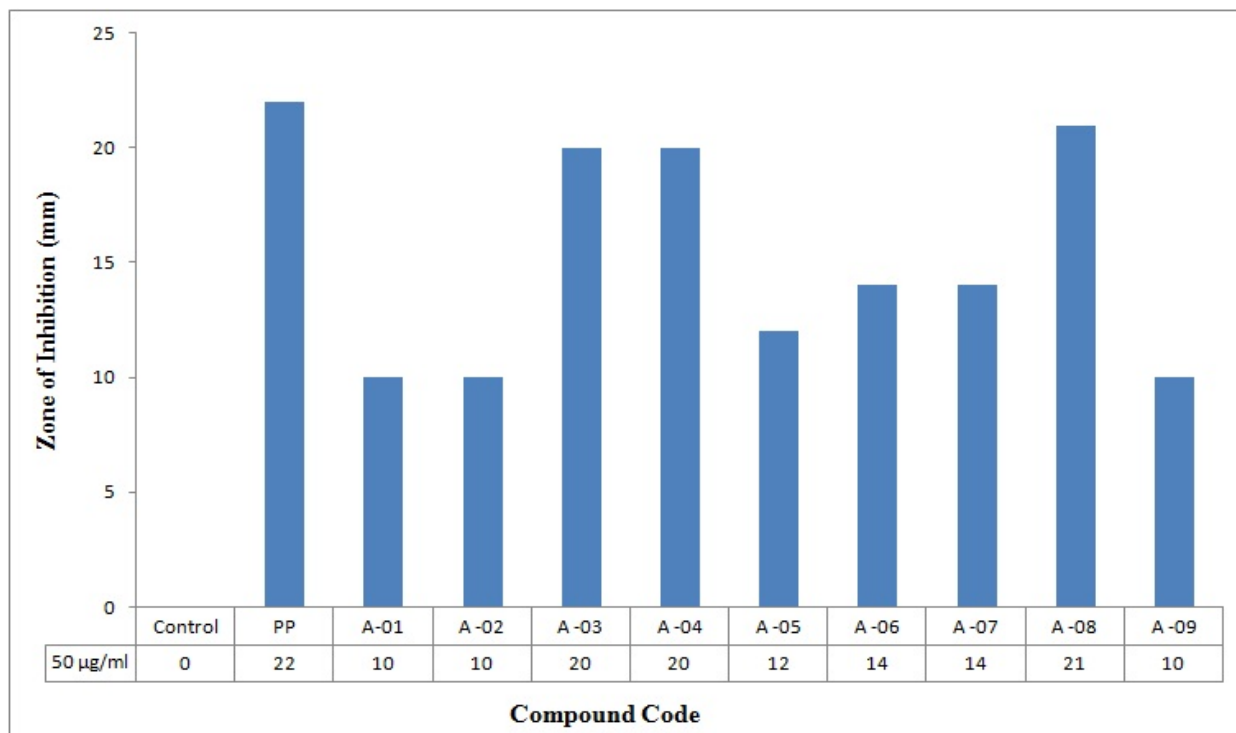


Figure 2: Result of zone of inhibition (mm) of novel synthesized compounds at 50 µg/ml

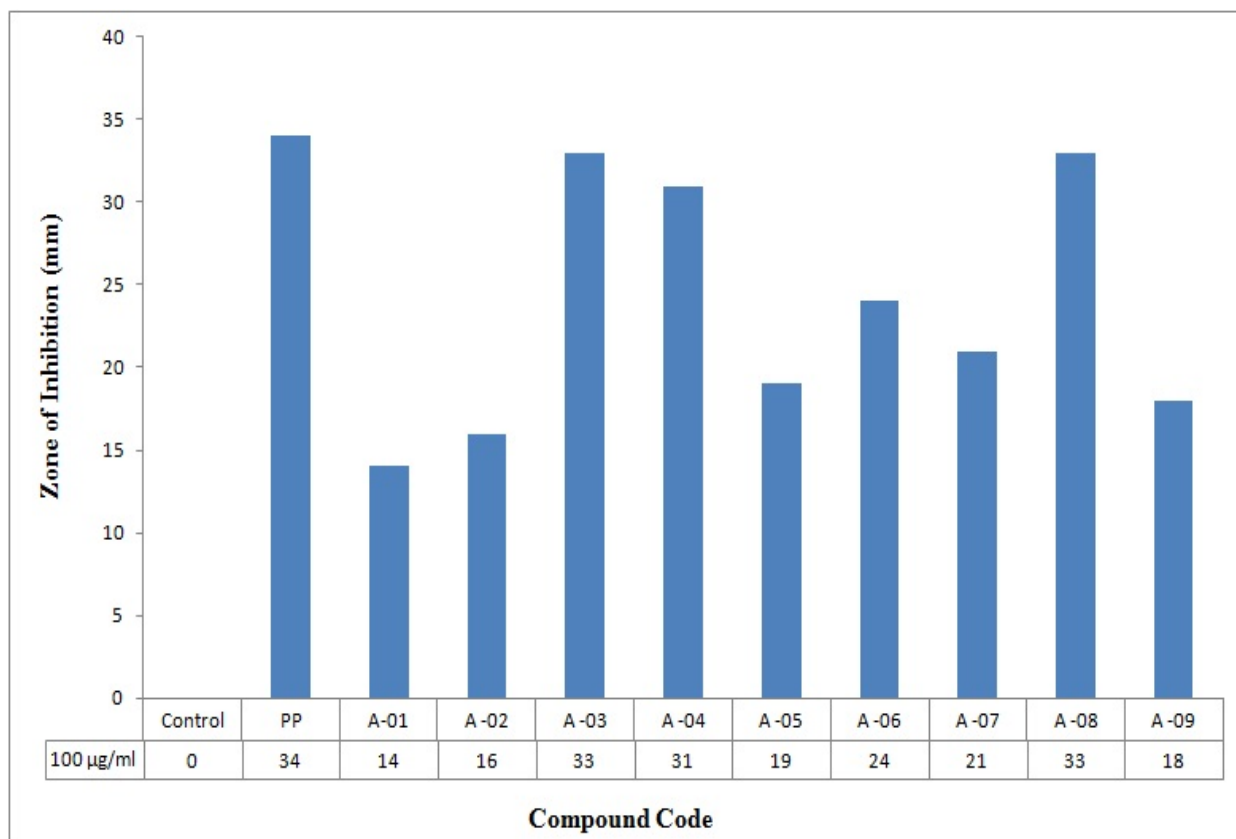


Figure 3: Result of zone of inhibition (mm) of novel synthesized compounds at 100 µg/ml

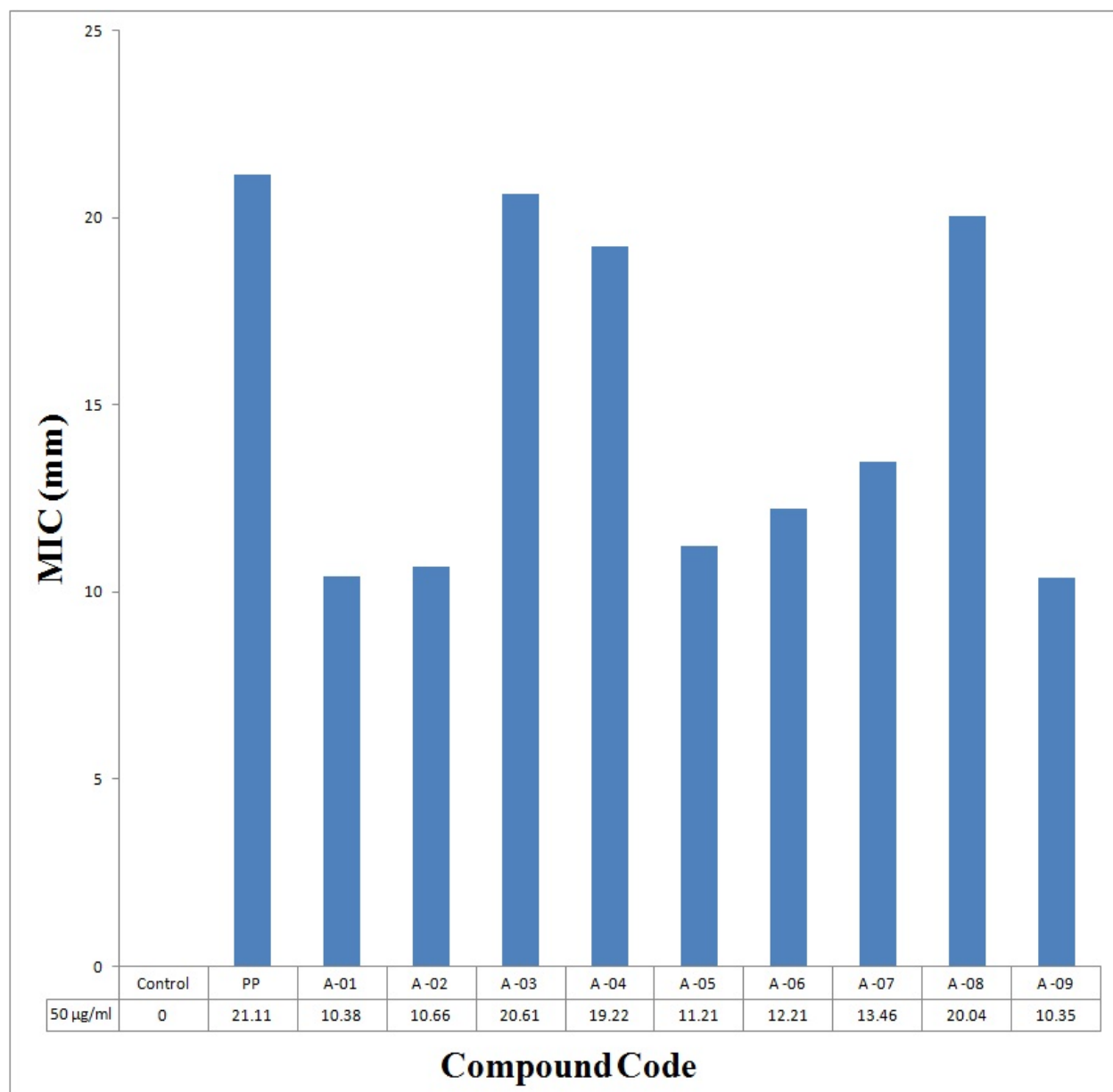


Figure 4: Result of minimum inhibitory concentration (MIC) of novel synthesized compounds at 50µg/ml

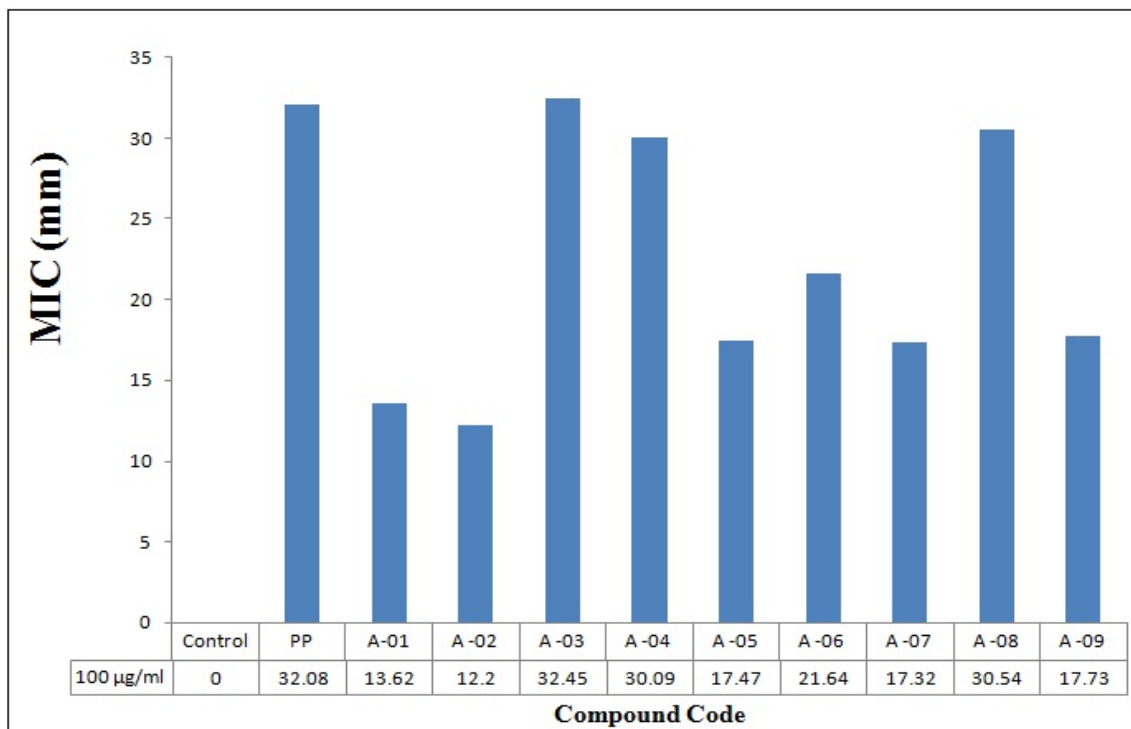


Figure 5: Result of minimum inhibitory concentration (MIC) of novel synthesized compounds at 100µg/ml

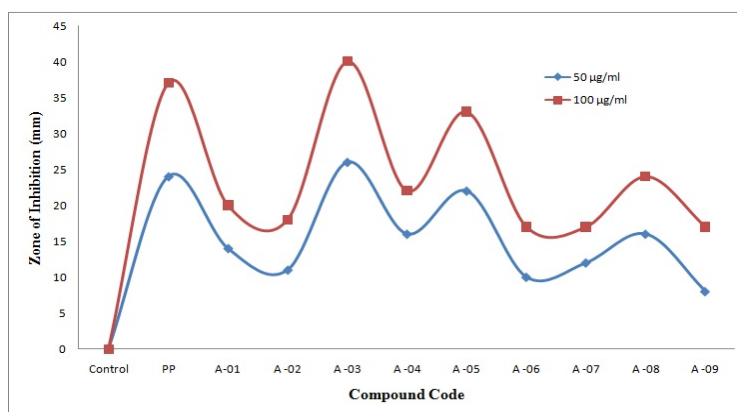


Figure 6: Comparative study of zone of inhibition (mm) of novel synthesized compounds at 50µg/ml and 100µg/ml

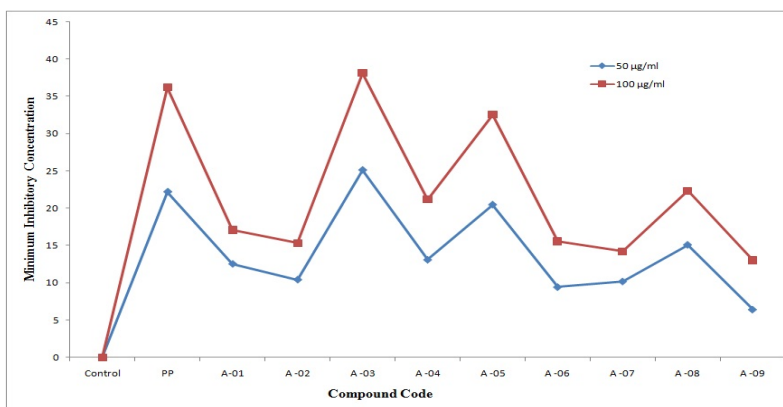


Figure 7: Comparative study of minimum inhibitory concentration of novel synthesized compounds at 50µg/ml and 100µg/ml

CONCLUSION

In the present work, hydroxy substituted novel benzothiazole derivatives were synthesized and screened for antibacterial activity against *S. pyogenes*. The paucity of data showed that compound A-03, A-04 and A-08 showed potent activity and could be considered for further clinical trials as antibacterial agents.

REFERENCES

- Bhawsar SB, Mane DV, Sinde DB, Shingare MS, Deokate AS and Congwane LV. Synthesis of some 8-[6'-substituted-1', 3'-benzothiazol-2'-yl] amino methyl] substituted hydroxyl coumarins and Evaluation of their antibacterial activity. *Indian journal of heterocyclic chemistry* 1996; 8:23-26.
- Yaseen A, Haitham H, Bahjat S, Ihsan H, Mohammad O, et al. Synthesis and in vitro antiproliferative activity of new benzothiazole derivatives. *ARKIVOC Journal* 2008; 15:225-38.
- Nagarajan SR, De CGA, Getman DP, Lu HF, Sikorski JA, Walker JL, et al. Replacement of the ureas moiety by benzothiazolesulfonamide provided inhibitors of HIV-1 protease with improved potency and antiviral activities. *Bioorganic and Medicinal Chemistry Letters* 2003; 11:4769-4773.
- Wells G, Bradshaw TD, Diana P, Seaton A, Shi DF, Westwell AD, et al. Synthesis and Anti-tumor activity of Benzothiazole Substituted Quinol Derivatives. *Bioorganic and Medicinal Chemistry Letters* 2000; 10:513-5.
- Latrofa A, Franco M, Lopodota A, Rosato A, Carone D, Vitali C. Structural modification and antimicrobial activity of N-cycloalkylidene-2, 3-dihydro-1, 3-benzothiazoles, N-cycloalkyl-2-acylalkylidene-2, 3-dihydro-1, 3-benzothiazoles. *II Farmaco Journal* 2005; 60:291-297.
- Dogruer DS, Unlu S, Sahin MF, Yesilada E. Synthesis of (2-benzothiazolone-3-yl and 2-benzothiazolone-3-yl) acetic acid derivatives and Evaluation of their Antinociceptive and Anti-inflammatory Activity. *IL Farmaco Journal* 1998; 53: 80-86.
- Cressier D, Prouillac C, Hernandez P, Amourette C, Diserbo M, Lion C, et al. Synthesis, antioxidant properties and radioprotective effects of new benzothiazoles and thiaziazoles. *Bioorganis and Medicinal Chemistry* 2009; 17:5275.
- Moreno-Diaz H, Villalobos-Molina R, Ortiz-Andrade R, Diaz-Coutiño D, Medina-Franco JL, Webster SP, et al. Antidiabetic activity on N-(6- substituted-1, 3-benzothiazol-2-yl) benzenesulfonamides. *Bioorganic and Medicinal Chemistry Letters* 2008; 18:2871-2877.
- Barde AR, Barsu HK, Bobade AS. Synthesis of 5, 6-Disubstituted 2-(Substituted Phenyl Carboxamido) Benzothiazoles As Potential Anthelmintic and Anti-Microbial agents. *Indian Drugs* 1998; 35:554-557.
- Tapia RA, Prieto Y, Pautet F, Domard M, Sarciron ME, Walchshofer N, et al. Synthesis and Antileishmanial Activity of Indoloquinones Containing a Fused Benzothiazole Ring. *European Journal of Organic Chemistry* 2002; 17:4005-4010.
- Siddiqui N, Rana A, Khan SA, Haque SE, Alam MS, Ahsana W. Anticonvulsant and Toxicity Evaluation of Newly Synthesized 1-[2-(3,4-disubstituted phenyl)-3-chloro-4-oxoazetid-1-yl]-3-(6-substituted-1,3-benzothiazol-2-yl) ureas. *Acta Chimica Slovenica* 2009; 56:462-469.
- Mollmann U. Synthesis of 2-Benzylsulfanyl Derivatives of Benzoxazoles and Benzothiazoles and Evaluation of in vitro activity against *M. tuberculosis* and non-tuberculous Mycobacteria. *Bioorganic and Medicinal Chemistry Letters* 2002; 12:3275-3278.
- Danzeisen R, Schwalenstoecker B, Gillardon F. Targeted antioxidative and neuroprotective properties of the dopamine agonist pramipexole and its nondopaminergic enantiomer SND919CL2x [(+)-2-amino-4,5,6,7-tetrahydro-6-L-propylamino-benzathiazole dihydrochloride]. *The Journal of Pharmacology and Experimental Therapeutics* 2006; 316:189-1899.
- Diouf O, Depreux P, Lesieur D, Poupaert J, Caignard D. Synthesis and evaluation of new 2-piperazinybenzothiazoles with high 5-HT1A and 5-HT3 affinities. *European Journal of Medicinal Chemistry* 1995; 30:715-721.
- Pandurangan A, Sharma A, Sharma N, Sharma PK and Visht S. Synthesis and structural studies of novel benzothiazole derivative and evaluation of their antimicrobial activity. *Der Pharma Chemica* 2010; 2: 316-324.
- Bhusari KP, Amnerkar Nd, Khedekar PB, Kale MK and Bhole RP. Synthesis and *in vitro* antimicrobial activity of some new 4-amino-N-(1,3-Benzothiazol-2-yl) benzene sulphonamide derivatives. *Asian Journal of Research in Chemistry* 2008; 1: 53-58.
- Sreenivasa GM, Jyachandran E, Shivakumar B, Jayaraj KK and Kumar V. Synthesis of bioactive molecule fluoro benzothiazole comprising potent heterocyclic moieties for anthelmintic activity. *Archives of Pharmaceutical Science and Research* 2009; 1: 150-157.
- O'Loughlin RE, Roberson A, Cieslak PR, Lynfield R, Gershman K, Craig A et al. The epidemiology of invasive group A streptococcal infection and potential vaccine implications: United States, 2000-2004. *Clinical Infectious Disease* 2007; 45:853-862.
- O'Grady KA, Kelpie L, Andrews RM, Curtis N, Nolan TM, Selvaraj G et al. The epidemiology of invasive group A streptococcal disease in Victoria, Australia. *Medical Journal of Australia* 2007; 186:565-569.
- Tyrrell GJ, Lovgren M, Kress B, Grimsrud K. Invasive group A streptococcal disease in Alberta, Canada in 2000 to 2002. *Journal of Clinical Microbiology* 2005; 43(4):1678-1683.
- Hollm-Delgado MG, Allard R, Pilon PA. Invasive group A streptococcal infections, clinical manifestations and their predictors. *Emerging Infectious Disease* 2005; 11(1):77-82.
- Stockmann C, Ampofo K, Hersh AL, et al. Evolving Epidemiologic Characteristics of Invasive Group A Streptococcal Disease in Utah. *Clinical Infectious Diseases* 2012; 55(4):479-487.
- Ekelund K, Skinhoj P, Madsen J, Konradsen HB. Invasive group A, B, C and G streptococcal infections in Denmark 1999-2002: epidemiological and clinical aspects. *Clinical Microbiology and Infection* 2005; 11 :569-576.
- Eriksson BK, Norgren M, McGregor K, Spratt BG, Normark BH. Group A streptococcal infections in Sweden: a comparative study of invasive and noninvasive infections and analysis of dominant T28 emm28 isolates. *Clinical Infectious Disease* 2003; 37:1189-1193.
- Demers B, Simor AE, Vellend H, Schlievert PM, Byrne S, Jamieson F et al. Severe invasive group A streptococcal infections in Ontario, Canada: 1987-1991. *Clinical Infectious Disease* 1993; 16:792-800.
- Bucher A, Martin PR, Hoiby EA, Halstensen A, Odegaard A, Hellum KB et al. Spectrum of disease in bacteraemic patients during a *Streptococcus pyogenes* serotype M-1 epidemic in Norway in 1988. *European journal of clinical microbiology & infectious diseases* 199; 11:416-426.
- Stromberg A, Romanus V, Burman LG. Outbreak of group A streptococcal bacteremia in Sweden: an epidemiologic and

- clinical study. *Journal of Infectious Disease* 1991; 164:595-598.
28. Cone LA, Woodard DR, Schlievert PM, Tomory GS. Clinical and bacteriologic observations of a toxic shocklike syndrome due to *Streptococcus pyogenes*. *New England Journal of Medicine* 1987; 317:146-149.
29. Veasy LG, Wiedmeier SE, Orsmond GS, Ruttenberg HD, Boucek MM, Roth SJ et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. *New England Journal of Medicine* 1987; 316:421-427.
30. Martin PR, Hoiby EA. Streptococcal serogroup A epidemic in Norway 1987-1988. *Scandinavian Journal of Infectious Diseases* 1990; 22:421-429.
31. Andersen MM, Ronne T. Group A streptococcal bacteraemias in Denmark 1987-89. *Journal of Infection* 1995; 31:33-37.

Cite this article as:

Akhilesh Gupta. Antibacterial activity of novel hydroxy substituted benzothiazole derivatives against *Streptococcus pyogenes*. *Int. Res. J. Pharm.* 2018;9(6):207-215
<http://dx.doi.org/10.7897/2230-8407.096118>

Source of support: Nil, Conflict of interest: None Declared

Disclaimer: IRJP is solely owned by Moksha Publishing House - A non-profit publishing house, dedicated to publish quality research, while every effort has been taken to verify the accuracy of the content published in our Journal. IRJP cannot accept any responsibility or liability for the site content and articles published. The views expressed in articles by our contributing authors are not necessarily those of IRJP editor or editorial board members