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Research Article

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

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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 applications[1-5]. 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 antihypoxic[6-9]. 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 thiobenzanilides[10]. 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 thiobenzanilides[11-17]. 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 England[18-21]. Like other members of the family *Streptococcacae*, *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 children[22]. 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 tissues[20-23]. These infections cause over ten million outpatient visits and nearly a half-million hospital admissions per year in the world[24-31]. 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). ^{1}HNMR Bruker (AM 400), Japan was used using $CDCL_3$ 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 85^0C 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 85^0C 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 recrystalized from benzene, ethanol of (1:1) to yeild 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 recrystalized 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 recrystalized 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-264-269^0C, Rf value-0.45, IR Range-1469cm^{-1}Ar C=C, 1648cm^{-1}C=O, 1255cm^{-1}C-S, 1540cm^{-1}C-NO_2, 3002cm^{-1}C-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-274-278^0C, Rf value-0.39, IR Range-1454cm^{-1}Ar C=C, 1640cm^{-1}C=O, 1257cm^{-1}C-S, 1575cm^{-1}C-NO_2. 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-260-265^0C, Rf value-0.33, IR Range-1478cm^{-1}Ar C=C, 1668cm^{-1}C=O, 1221cm^{-1}C-S, 1563cm^{-1}C-NO_2. 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-258-264^0C, Rf value-0.46, IR Range-1425cm^{-1}Ar C=C, 1653cm^{-1}C=O, 1241cm^{-1}C-S, 1560cm^{-1}C-NO_2. 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-269-273^0C, Rf value-0.44, IR Range-1422cm^{-1}Ar C=C, 1665cm^{-1}C=O, 1240cm^{-1}C-S, 1551cm^{-1}C-NO_2. 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^{0}C, Rf value-0.48, IR Range-1433cm^{-1}Ar C=C, 1619cm^{-1}C=O, 1234cm^{-1}C-S, 1539cm^{-1}C-NO_2. 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^{0}C, Rf value-0.50, IR Range-1455cm^{-1}Ar C=C, 1612cm^{-1}C=O, 1234cm^{-1}C-S, 1533cm^{-1}C-NO_2 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^{0}C, Rf value-0.48, IR Range-1417cm^{-1}Ar C=C, 1662cm^{-1}C=O, 1212cm^{-1}C-S, 1512cm^{-1}C-NO_2. 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^{0}C, Rf value-0.54, IR Range-1426cm^{-1}Ar C=C, 1630cm^{-1}C=O, 1238cm^{-1}C-S, 1537cm^{-1}C-NO_2. 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^{0}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^{0}C -10^{0}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^{0}C for 18-24 hours. After the incubation period, the petriplates were observed for zone of inhibition by using verniar 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-organisns is 10^6 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 37ºC 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 ^{1}HNMR 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-NO_2 was considered. In case of structure elucidation of by ^{1}HNMR 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*

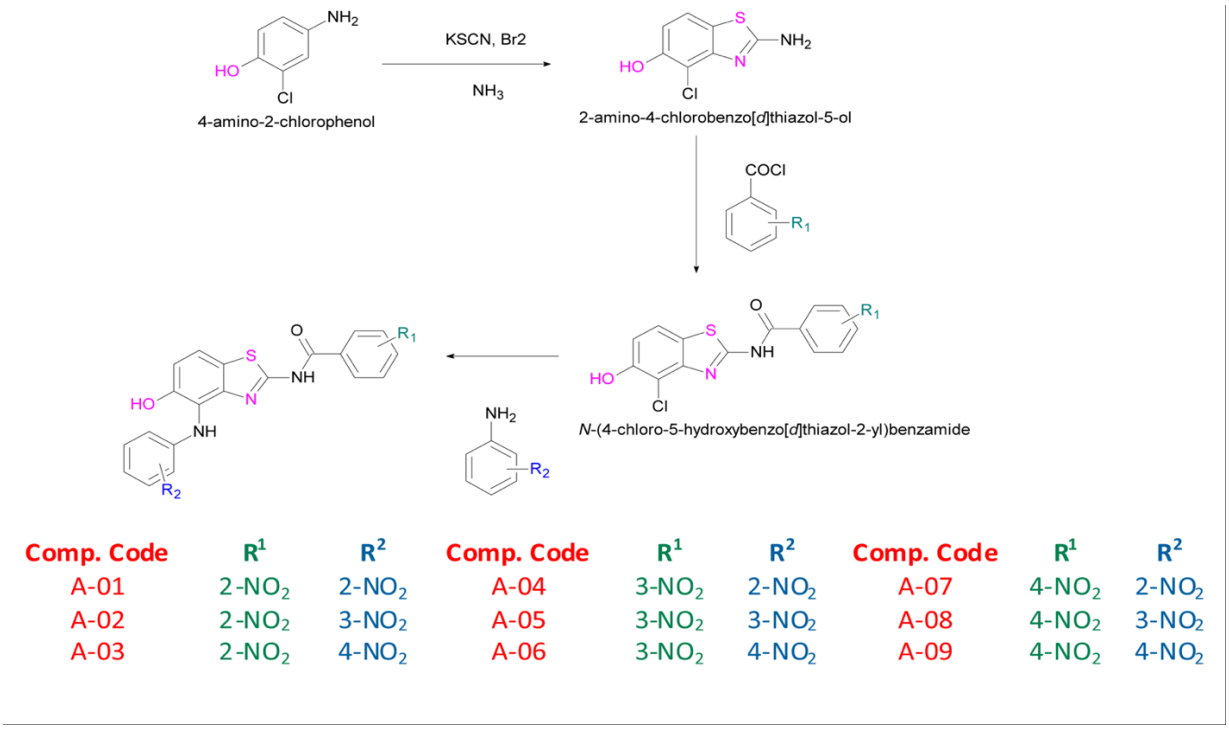
Compound Code	Zone of Inhibition (mm)*	
	Streptococcus pyogenes	
	50 µg/ml	100 µg/ml
Procaine penicillin (PP)	22	34
A-01	10	14
A -02	10	16
A -03	20	33
A -04	20	31
A -05	12	19
A -06	14	24
A -07	14	21
A -08	21	33
A -09	10	18
Control	0	0

*Each value is the mean of three replicates

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

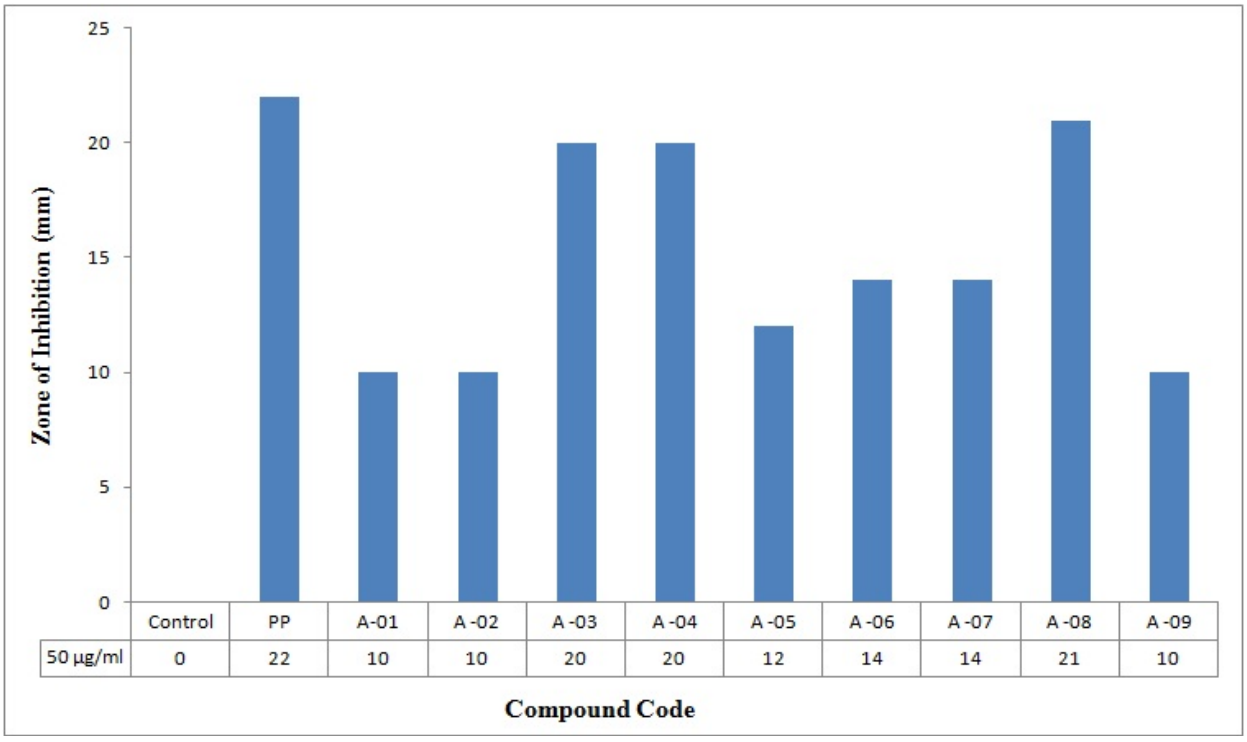
Compound Code	Minimum inhibitory concentration (MIC) µg/ml ± SD*	
	Streptococcus pyogenes	
	50 µg/ml	100 µg/ml
Procaine penicillin (PP)	21.11 ± 0.62	32.08 ± 0.22
A-01	10.38 ± 0.15	13.62 ± 0.25
A -02	10.66 ± 0.45	12.20 ± 0.24
A -03	20.61 ± 0.29	32.45 ± 0.75
A -04	19.22 ± 0.09	30.09 ± 042
A -05	11.21 ± 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



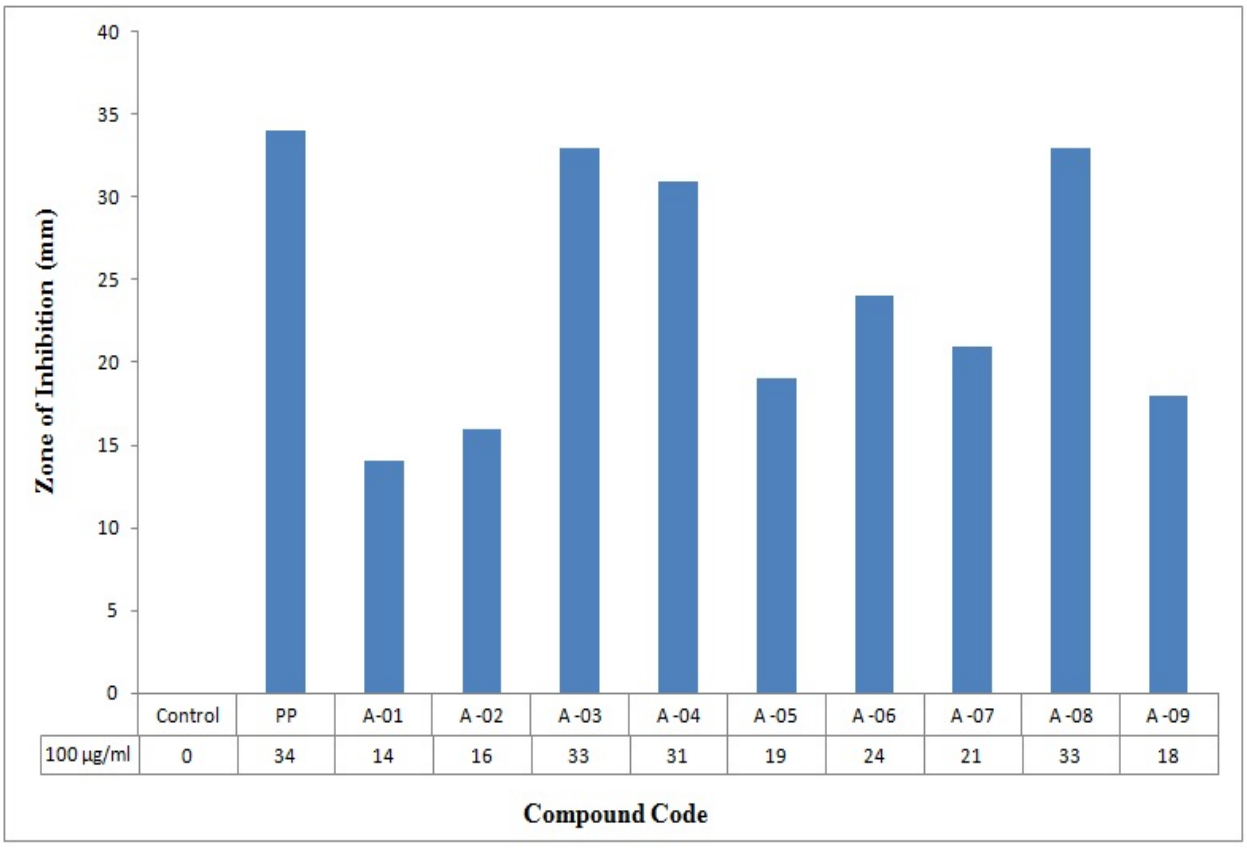
Comp. Code	R^1	R^2	Comp. Code	R^1	R^2	Comp. Code	R^1	R^2
A-01	2-NO_2	2-NO_2	A-04	3-NO_2	2-NO_2	A-07	4-NO_2	2-NO_2
A-02	2-NO_2	3-NO_2	A-05	3-NO_2	3-NO_2	A-08	4-NO_2	3-NO_2
A-03	2-NO_2	4-NO_2	A-06	3-NO_2	4-NO_2	A-09	4-NO_2	4-NO_2

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



	Control	PP	A-01	A -02	A -03	A -04	A -05	A -06	A -07	A -08	A -09
50 µg/ml	0	22	10	10	20	20	12	14	14	21	10

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



	Control	PP	A-01	A -02	A -03	A -04	A -05	A -06	A -07	A -08	A -09
100 µg/ml	0	34	14	16	33	31	19	24	21	33	18

Figure 3: Result of zone of inhibition (mm) of novel synthesized compounds at100 µg/ml

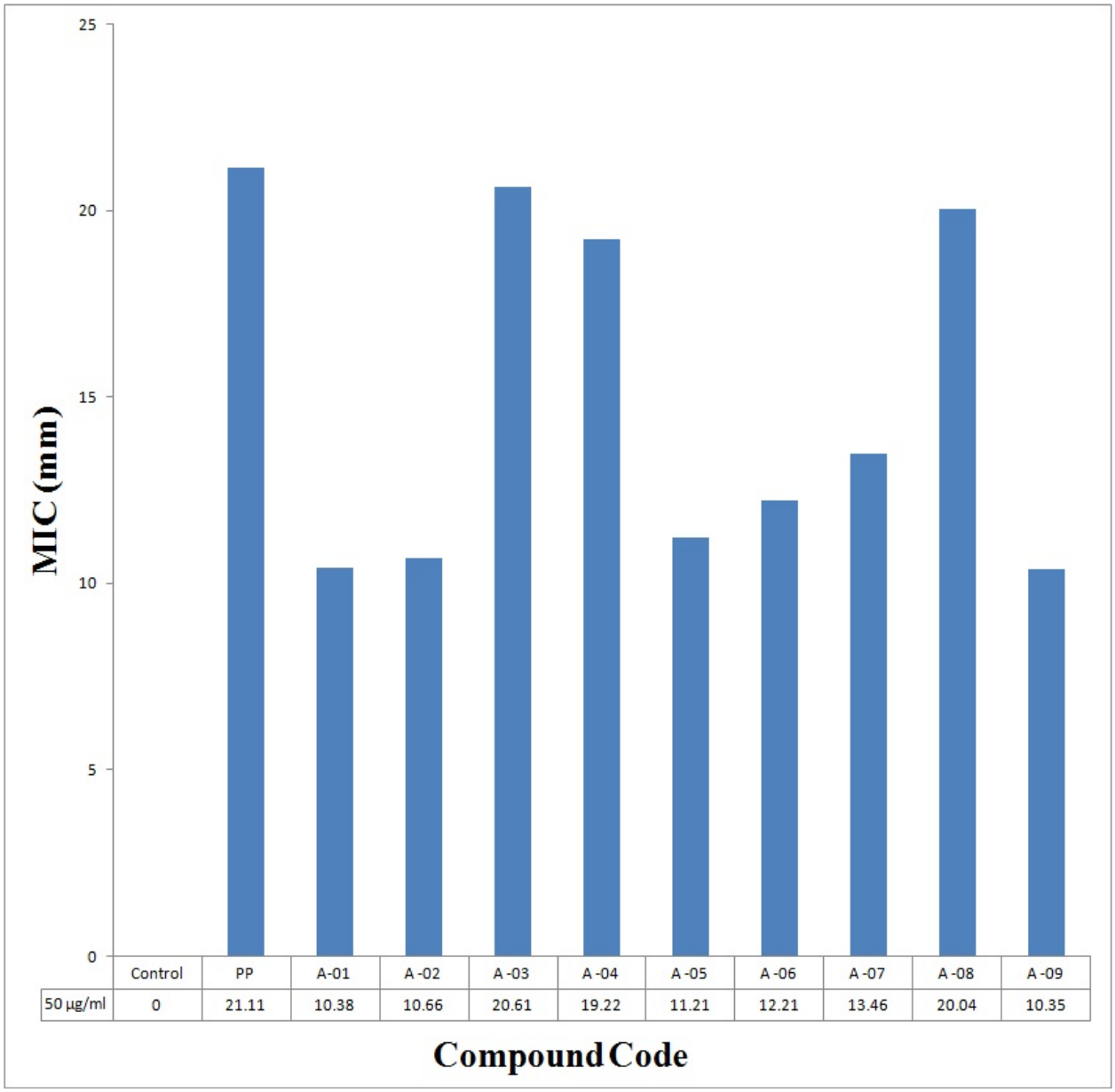


Figure 4: Result of minimum inhibitory concentration (MIC) of novel synthesized compounds at 50µg/ml

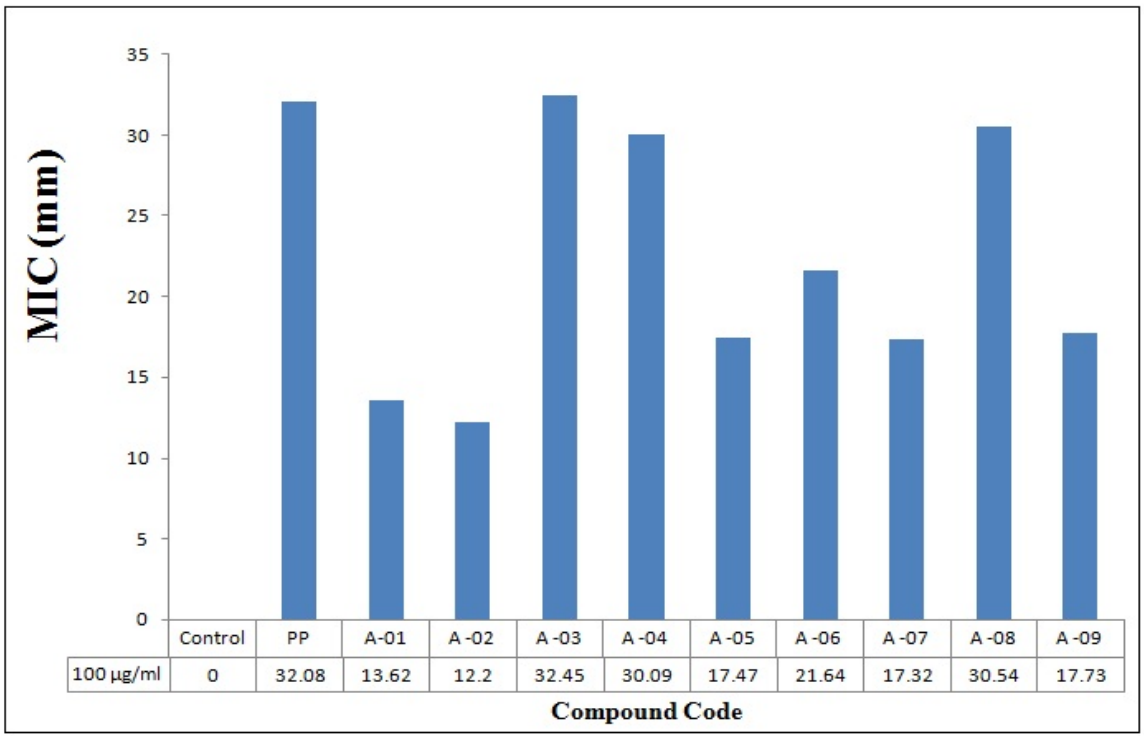


Figure 5: Result of minimum inhibitory concentration (MIC) of novel synthesized compounds at 100µg/ml

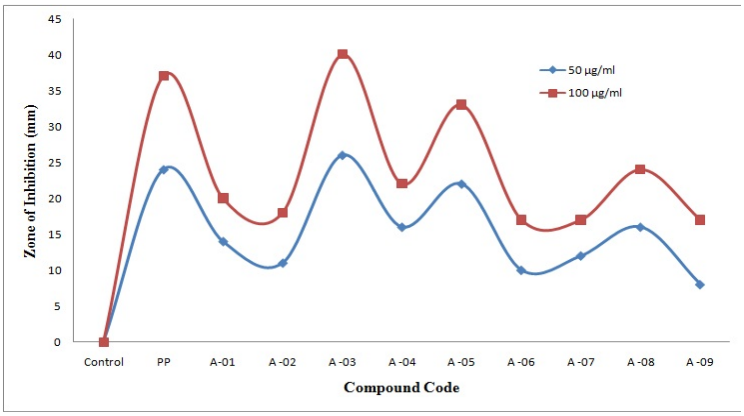


Figure 6: Comparative study of zone of inhibition (mm) of novel synthesized compounds at 50µg/ml and 100µg/ml

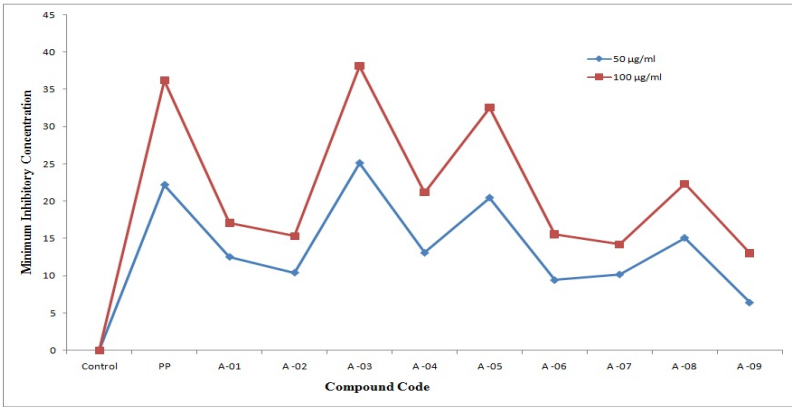


Figure 7: Comparative study of minimum inhibitory concentration of novel synthesized compounds at 50µg/ml and 100µg/ml

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.

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