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Synthesis of Novel Methoxy Substituted Benzothiazole Derivatives and Antibacterial activity against Streptococcus Pyogene

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ABSTRACT: Streptococcus (S) pyogenes is a Gram-positive facultative anaerobic organism which occurs in chains or in pairs and rarely cause life-threatening infection. 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. 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 methoxy substitution at benzothiazole. Methoxy substituted benzothiazole derivatives were synthesized by reaction of 3-chloro-4-methoxy-aniline with potassium thiocyanate under temperature control and presence of bromine in glacial acetic acid and ammonia. Substituted nitrobenzamides then synthesized by condensation of, 2-amino-4-chloro-5-methoxy-benzothiazole with 2(3or4)-nitrobenzoylchloride acid in presence of dry pyridine and acetone. Finally, newly synthesized derivatives (K-01 to K-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 spectral study. Antibacterial activity was performed against S. pyogenes by cup plate method (diffusion technique) using procaine penicillin as standard. Compound K-01 showed potent antibacterial activity against S. pyogenes at both concentrations 50µg/ml and 100µg/ml as compared to standard.

Keywords: Methoxy-benzothiazole; Benzothiazole; Antibacterial activity; 2-substituted benzothiazole; Cyclization of benzothiazole and Streptococcus pyogenes.

INTRODUCTION: Severe infections caused by the Lancefield group especially Streptococcus (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.[1-5] 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 was detected in Gloucestershire, in the South West of England.[6-9] Like other members of the family Streptococcacae, streptococci are Gram-positive facultative anaerobic organisms which occur in chains or in pairs. In Theodor Billroth proposed name for Streptococcus through the identification 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. Different M-types are known to favour mucosal versus cutaneous sites, the latter constituting the higher-numbered types in 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 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.[10-11] These infections cause over ten million outpatient visits and nearly a half-million hospital admissions per year in the world.[12-14] 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[9-13]. 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.[14-17] 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 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[18]. 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 substituted thiobenzanilides.[19-26] The present work concern with synthesis of methoxy and aryl-nitro substituted benzothiazole derivatives followed by antibacterial activity for structure activity relationship.

MATERIAL AND METHODS:

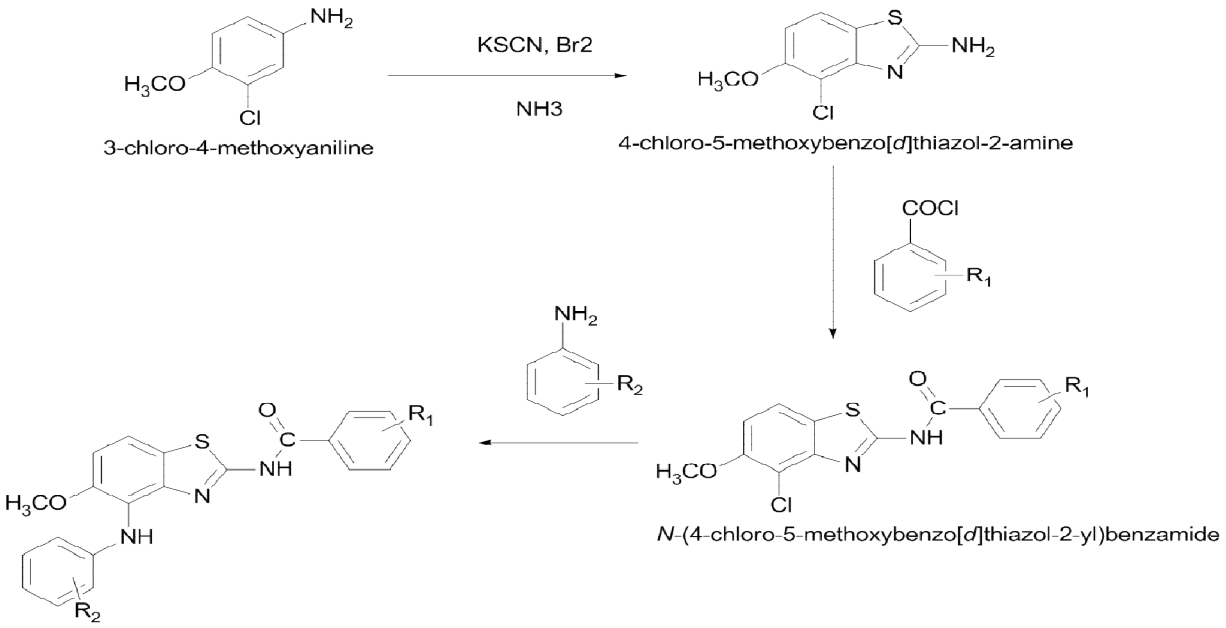
Synthesis of substituted benzothiazole (Compound Code 1-KB): Synthesis of substituted benzothiazole nucleus was achieved by adding 8gm (0.08mol) of potassium thiocyanate and 1.45g (0.01 mol) of 3-choloro-4-methoxy-aniline into 20 ml cooled glacial acetic acid in such a way that the temperature not exceeded 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 get substituted benzothiazole.

Synthesis of nitrobenzamide (Compound code 2-KB, 3-KB, and 4-KB): 5.36g (0.026mol) of 2-(3 or 4)-nitrobenzoylchloride was dissolved in dry acetone. Product 1-KB 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-KB, 3-KB and 4-KB.

Synthesis of compound K-01 to K-09: 0.008 mol of 2 (3 or 4) nitro-substituted aniline was refluxed with 2.7g (0.0075 mol) of compound 2-KB, 3-KB and 4-KB 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 K-01 to K-09 (Figure 1).

Analytical Characterization: Thin layer chromatography (TLC) was used to monitor reaction progress, completion and identification of newly synthesized compounds from starting material using solvent system butanol: ethyl acetate: benzene [1:2:1] and detection performed by exposing them to iodine vapours. The melting point of compounds was determined using open capillaries method. Structure elucidation of compounds was done by IR and ^{1}HNMR spectral study. SHIMADZU (8400S) used for IR spectral study (KBr pellet technique). For the structure elucidation using IR, frequency range for Ar-C=C, C=O, C-S, C-NO_2 were considered. Bruker AM 400 ^{1}H NMR instrument (at 400 MHz) was used using $CDCL_3$ as a solvent and tetramethoxysilane (TMS) as an internal standard. For structure elucidation by ^{1}HNMR, NH proton that characterized benzothiazole was considered.



Comp. Code	R1	R2	Comp. Code	R1	R2	Comp. Code	R1	R2
K-01	2-NO2	2-NO2	K-04	3-NO2	2-NO2	K-07	4-NO2	2-NO2
K-02	2-NO2	3-NO2	K-05	3-NO2	3-NO2	K-08	4-NO2	3-NO2
K-03	2-NO2	4-NO2	K-06	3-NO2	4-NO2	K-09	4-NO2	4-NO2

Figure 1: Synthetic scheme.

Antibacterial activity against S. pyogenes using procaine penicillin as standard: The standard drug and synthesized compounds were dissolved in minimum quantity of dimethyl 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. Dimethyl 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 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.

RESULTS AND DISCUSSION: Benzothiazole contains sulphur and nitrogen as heteroatom but imparts biological activity while substitution at C-2 position. In the present work, methoxy 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. The novel derivatives (K-01 to K-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 rarely acquired resistance developed by compounds bearing nitro group. TLC, melting point, IR and ^{1}HNMR were used for analytical characterization. In the TLC, the distance traveled by compound K-01 to K-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 7.0-8.0 ppm is observed and consider as benzothiazole in all the synthesized compounds (Tbale-1). Antibacterial activity performed at two concentration 50µg/ml and 100µg/ml using procaine penicillin as a standard drug against *S. pyogenes*. Compound K-01 showed potent antibacterial activity against *S. pyogenes* at both concentrations 50µg/ml and 100µg/ml as compared to standard (Table-2).

Table 1: Analytical characterization of synthesized compounds.

Comp. Code	% Yield	Mel. Point (^{0}C)	TLC (Rf)	IR Spectral Study	^{1}HNMR Spectral Study (400Hz, DMSO-d6)
K-01	71	261	0.41	1456cm^{-1}Ar C=C, 1632cm^{-1}C=O, 1245cm^{-1}C-S, 1544cm^{-1}C-NO_2.	δ 4.61, (s, 1H, NH), δ 3.31(s, 3H, CH_3), δ 7.10-7.72 (m, 10H, Ar-H), δ 8.89 (s, 1H, C-NH)
K-02	72	260	0.43	1454cm^{-1}Ar C=C, 1640cm^{-1}C=O, 1257cm^{-1}C-S, 1575cm^{-1}C-NO_2.	δ 4.52, (s, 1H, NH), δ 3.39(s, 3H, CH_3), δ 7.18-7.85 (m, 10H, Ar-H), δ 9.10 (s, 1H, C-NH)
K-03	68	266	0.46	1454cm^{-1}Ar C=C, 1652cm^{-1}C=O, 1241cm^{-1}C-S, 1523cm^{-1}C-NO_2.	δ 4.55, (s, 1H, NH), δ 3.30(s, 3H, CH_3), δ 7.19-7.62 (m, 10H, Ar-H), δ 8.80 (s, 1H, C-NH)
K-04	68	275	0.50	1421cm^{-1}Ar C=C, 1665cm^{-1}C=O, 1243cm^{-1}C-S, 1537cm^{-1}C-NO_2.	δ 4.62, (s, 1H, NH), δ 3.42(s, 3H, CH_3), δ 7.22-7.60 (m, 10H, Ar-H), δ 8.95 (s, 1H, C-NH)
K-05	69	256	0.48	1443cm^{-1}Ar C=C, 1626cm^{-1}C=O, 1222cm^{-1}C-S, 1543cm^{-1}C-NO_2	δ 4.56, (s, 1H, NH), δ 3.44(s, 3H, CH_3), δ 7.21-7.80 (m, 10H, Ar-H), δ 8.96 (s, 1H, C-NH)
K-06	79	271	0.42	1421cm^{-1}Ar C=C, 1615cm^{-1}C=O, 1212cm^{-1}C-S, 1554cm^{-1}C-NO_2	δ 4.65, (s, 1H, NH), δ 3.41(s, 3H, CH_3), δ 7.09-7.66 (m, 10H, Ar-H), δ 9.15 (s, 1H, C-NH)
K-07	65	269	0.52	1423cm^{-1}Ar C=C, 1626cm^{-1}C=O, 1220cm^{-1}C-S, 1540cm^{-1}C-NO_2	δ 4.60, (s, 1H, NH), δ 3.30(s, 3H, CH_3), δ 7.18-7.60 (m, 10H, Ar-H), δ 8.80 (s, 1H, C-NH)
K-08	67	264	0.40	1421cm^{-1}Ar C=C, 1615cm^{-1}C=O, 1212cm^{-1}C-S, 1554cm^{-1}C-NO_2	δ 4.65, (s, 1H, NH), δ 3.40(s, 3H, CH_3), δ 7.10-7.68 (m, 10H, Ar-H), δ 8.83 (s, 1H, C-NH)
K-09	60	269	0.56	1458cm^{-1}Ar C=C, 1664cm^{-1}C=O, 1244cm^{-1}C-S, 1552cm^{-1}C-NO_2	δ 4.66, (s, 1H, NH), δ 3.44(s, 3H, CH_3), δ 7.20-7.60 (m, 10H, Ar-H), δ 8.85 (s, 1H, C-NH)

Table 2: Result of antibacterial activity.

Compound Code	Streptococcus pyogenes	
	50 µg/ml	100 µg/ml
Procaine Penicillin (PP)	24	36
K-01	26	34
K-02	07	11
K-03	12	18
K-04	08	13
K-05	08	15
K-06	10	16
K-07	05	12
K-08	13	19
K-09	15	22

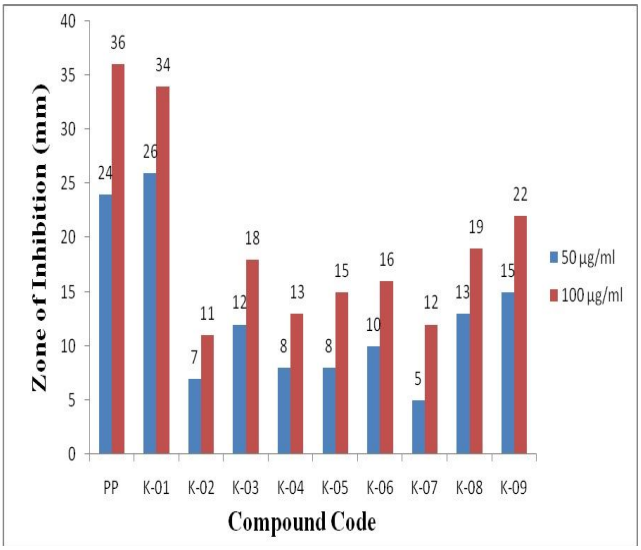


Figure 2: Comparative study of novel synthesized derivatives against S. pyogenes.

CONCLUSION: In the present work, methoxy substituted novel benzothiazole derivatives were synthesized and screened for antibacterial activity against *S. pyogenes.* The paucity of data showed that compound K-01 showed potent activity and could be considered for further clinical trials as antibacterial agents.

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