Research Article

Synthesis of Novel Methoxy Substituted Benzothiazole derivatives and antibacterial activity against *Staphylococcus epidermidis*

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Abstract

Objective: *Staphylococcus (S.) epidermidis* basically characterized as an innocuous commensal bacterium and as an important human pathogen that is responsible to one of the leading causes of infections especially on human skin. The present study was aimed to perform evaluation against infection caused by *S. epidermidis* for the molecules belonging benzothiazole derivatives have great importance in heterocyclic chemistry because of its potent and significant biological activities especially methoxy substitution at benzothiazole. **Materials and Methods:** 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 spectra. Antibacterial activity was performed against *S. epidermidis* by cup plate method (diffusion technique) using procaine penicillin as standard. **Results:** Methoxy substituted benzothiazole derivatives comprising nitro group were synthesized and characterized by using analytical techniques. The synthesized derivatives screened for antibacterial activity. Compound K-03 and K-8 showed potent antibacterial activity against *S. epidermidis* at both concentrations 50µg/ml and 100µg/ml as compared to standard. **Conclusion:** Synthesis and antibacterial activity of novel methoxy substituted derivatives with nitro substitution were performed to established structure activity relation. As per the result obtain after antibacterial activity compound K-03 and K-08 showed prominent activity against *S. epidermidis*.

***Keywords*:** Methoxy-benzothiazole, Benzothiazole, antibacterial, 2-substituted benzothiazole, *Staphylococcus epidermidis*

Introduction

Staphylococcus (S) epidermidis has been characterized as an innocuous commensal bacterium of human skin and currently, consider as an important human pathogen that is responsible to for one of the leading causes of infections. In the field of research toward Staphylococcus, the majority of research has been reported for the understanding of Staphylococcus infections but till date information related to infection caused by coagulase-negative Staphylococci (CoNS) is limited even the mechanism for how the host responds to the bacteria is also been not cleared. Since *S. epidermidis*, a member of the coagulase-negative Staphylococci, is an important commensal organism of the human skin and mucous membranes; and there is emerging evidence of its benefit for human health in fighting off harmful microorganisms (Bearman and Wenzel, 2005; Cerca et al., 2006; Cheung et al., 2014) However, *S. epidermidis* can cause opportunistic infections, which include particularly biofilm-associated infections on indwelling medical devices. These often can disseminate into the bloodstream; and in fact, *S. epidermidisis* the most frequent cause of nosocomial sepsis. The increasing use of medical implants and the dramatic shift in the patient demographic population in recent years have contributed significantly to the rise of *S. epidermidis* infections. Furthermore, treatment has been complicated by the emergence of antibiotic-resistant strains (Grice et al., 2009;

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Hajjar et al., 2001). Today, *S. epidermidis* is a major nosocomial pathogen posing significant medical and economic burdens. CoNS are an integral part of the normal flora on the human skin and mucous membranes, and preferentially colonize moist areas. *S. epidermidis*, the most common CoNS species recovered from clinical cultures, colonizes the armpit, groin, anterior nares, conjunctiva, toe webs, and perineal area (Kloos and Musselwhite, 1975; Belkaid and Tamoutounour, 2016). While usually innocuous or even beneficial colonizers, once the host epithelial barrier is compromised, CoNS such as *S. epidermidis* can cause serious infections. In fact, CoNS infections account for the majority of bacterial sepsis and foreign body-related infections, with *S. epidermidis* being the most significant species in that regard. The host immune response to *S. epidermidis*, the mechanism of immune tolerance, and the immune benefits that *S. epidermidis* commensals can provide, are just beginning to be unraveled. This review will provide the latest research on the host response to *S. epidermidis* as commensals, and as opportunistic bacteria in the context of biofilm and septic infections (Lai et al., 2010; Qin et al., 2017; Shiau et al., 1998; Strunk et al., 2010). 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 (Bradshaw et al., 1998; Alang et al., 2010; Suresh et al., 2010; Basavaraja et al., 2010; Vedavathi et al., 2010). 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 (Pandurangan et al., 2010; Rajeeva et al., 2009; Malik et al., 2009; Patel et al., 2010). 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 (Barot et al., 2010). 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 (Dua et al., 2010; Bhusari et al., 2010; Sathe et al., 2011; Sreenivasa et al., 2009; Venkatesh et al., 2009; Shashank et al., 2009; Kaur et al., 2010; Muttu et al., 2010). The present work concern with synthesis of methoxy and aryl-nitro substituted benzothiazole derivatives followed by antibacterial activity for structure activity relationship.

Materials 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)- nitroaniline 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.

Antibacterial activity against *S. epidermidis* using procaine penicillin as standard drug

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

Table 1. Analytical characterization of synthesized compounds

Compound 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, CONH)
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, CONH)
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, CONH)
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, CONH)
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, CONH
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, CONH
K-7	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, CONH)
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, CONH)
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, CONH

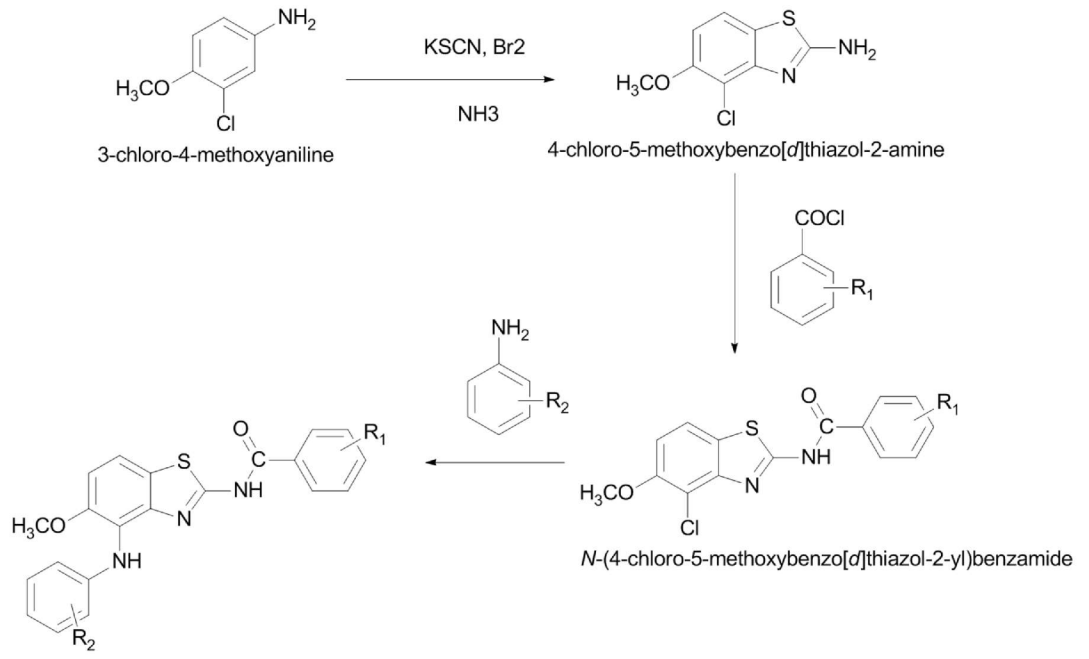
as rotating substituent at benzothiazole nucleus and derivatives were synthesized. The novel derivatives (K-01 to K-09) evaluated for antibacterial activity against *S. epidermidis*. In the present work nitro group consider as rotating basis on ortho, meta and para position. The reason behind considering nitro group as substituent is the fungi rarely acquire resistance. 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 (Table 1). Antibacterial activity performed at two concentration 50µg/ml and 100µg/ml using procaine penicillin as a standard drug against *S. epidermidis*. Compound K-03 and K-08 showed potent antibacterial activity against *S. epidermidis* at both concentrations 50µg/ml and 100µg/ml as compared to standard (Table 2). The comparative results of antibacterial activity were also given in figure 2.

Table2. Result of antibacterial activity

Compounds Code	*Staphylococcus epidermidis*	
	50 µg/ml	**100 µg/ml**
Procaine penicillin (PP)	21	36
K-1	18	30
K-2	06	16
K-3	21	34
K-4	11	19
K-5	05	10
K-6	13	20
K-7	07	12
K-8	20	35
K-9	14	22

Conclusion

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



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

Figure1. Synthetic scheme for synthesis of methoxy substituted benzothiazole derivatives

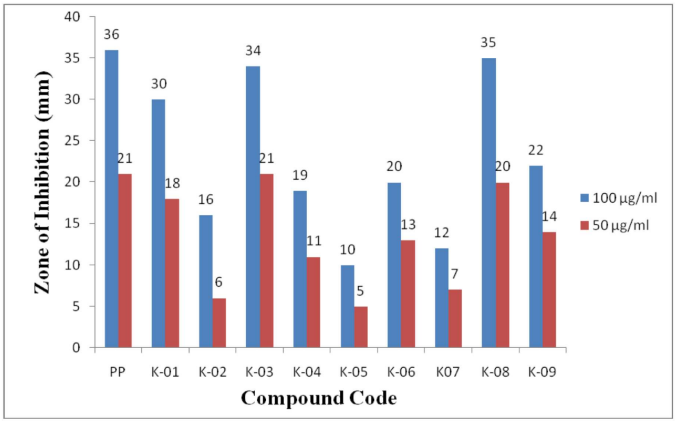


Figure 2. Comparative study of standard drug procaine penicillin (PP) and synthesized compounds

Conflicts of interest: Nil

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