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# Synthesis of novel benzothiazoles for anti-bacterial activity

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**ABSTRACT**

*A series of chlorine substituted 2-(3,5-dimethyl-pyrazol-1-yl)-6-fluoro-benzothiazoles were synthesized, by the reaction of 7-chloro-2-(3,5-dimethyl-pyrazol-1-yl)-6-fluoro-benzothiazole with various amines and alcohols in the presence of dimethyl formamide and anhydrous potassium carbonate, characterized by IR, NMR and elemental analysis. All the synthesized compounds were screened for their in vitro antibacterial activity against some Gram-positive and Gram-negative bacteria. The antibacterial study revealed that compounds* ***6(a–k)*** *have shown moderate activity against Gram-positive and Gram-negative organisms when compared with reference amoxicillin. Compound* ***6g, 6k*** *and* ***6f*** *were found to be more the most active against Gram-positive and Gram-negative bacteria.*

**Keywords:** Benzothiazole, Pyrazole, Anti-bacterial activity.

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## INTRODUCTION

Mankind has always been on the lookout for treating infections due to microorganisms. However, nature has always bounced back and newer varieties and strains of existing pathogenic bacteria and fungi have evolved. In addition to this, the bacteria and other microorganisms have developed resistance to the existing line of drugs. This gives us a challenge and ample scope for further investigating new molecules as anti-infective. As we all know, developing countries are mostly affected by health problems due to microbial infections. In a country like INDIA, where a majority of the population resides in rural areas with very minimal health care facilities and hygiene, it becomes necessary for us to work towards control of such problems [1].

Infectious as well as highly contagious microbial diseases are increasing with course of time round the world due to the emergence of new multidrug resistant bacteria [2]. The increasing incidence of bacterial resistance to large number of antibacterial agents such as glycopeptides, sulfonamides, β-lactams, nitroimidazoles, quinolones, tetracyclins, chloramphenicol and macrolides is becoming a major concern. In particular, the emergence of multiple drug resistant Gram positive and Gram-negative bacteria has caused life-threatening infectious diseases in many countries around the world [3].

Therefore, there is an increasing need to design new antibacterials with better activity profile. One way to battle with this challenge is the conscious usage of the currently marketed antibiotics and the other is to develop and screen new

chemical entities for antimicrobial activities. In view of this, it is imperative to discover new chemotherapeutic agents to prevent the emergence of resistance and ideally shorten the duration of therapy [2].

Molecules with benzothiazole moiety are attractive targets since they often exhibit diverse and important biological properties. These heterocyclics have shown different pharmacological activities such as gram-positive antibacterial agents, antibiotics, anti- parasitic, anti-inflammatory, lactase inhibitors, anti-stress, ulcer and anti-cancer agents [4] [5]. Due to the structural similarity with purine, antibacterial ability of these compounds manifested their competition with purines resulting in the distinct inhibition of the synthesis of nucleic acids and proteins inside the bacterial cell wall [6] [7].

## MATERIALS AND METHODS

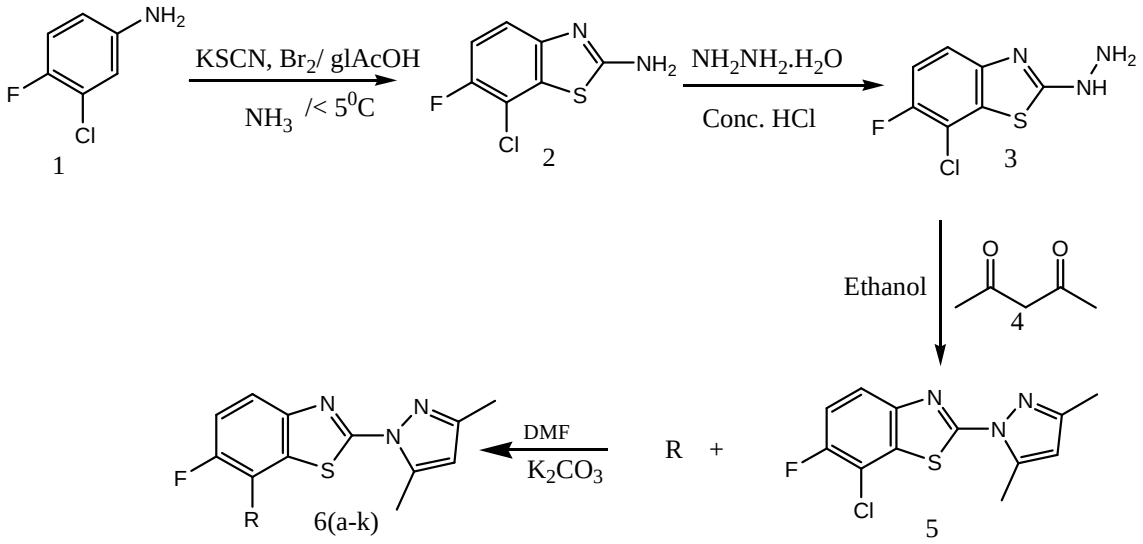
**Experimental:**
The melting points of the synthesized compounds were determined by open capillary method using Thiele's melting point tube or Thermionic melting point apparatus. The IR spectra of the synthesized compounds were recorded on a Fourier Transform Infra Red spectrometer (model Shimadzu 8700) in the range of 400-4000 $cm^{-1}$ as KBr pellets. The $^1H$ NMR spectra of the compounds were recorded using Bruker 200 spectrospin NMR spectrometer at Astra Zeneca Pharma India Limited, Bangalore & Bruker 400 spectrospin NMR spectrometer at Indian Institute of Science, Bangalore. The solvents used for NMR was $CDCl_3$ or DMSO- d6.

**Synthesis of 2-amino-7-chloro-6-fluorobenzothiazole (2):**
In a 250 ml 3 necked RBF fitted with a mechanical stirrer, addition funnel and a thermometer were placed glacial acetic acid (40 ml), potassium thiocyanate (40g, 2.4 mol) and 3-chloro-4-fluoroaniline (7.25g, 0.05 mol) [8]. The reactants were pre cooled to 0-5 $^{\circ}C$ using a freezing mixture. A solution of bromine (6 ml bromine in 24 ml glacial acetic acid) was added drop wise through the addition funnel with continuous stirring of the reactants and maintaining the temperature of the reaction between 0-5 $^{\circ}C$ during the course of addition. The mixture was further stirred between 0-5 $^{\circ}C$ for 2hrs and at room temperature for 10h, allowed to stand overnight during which an orange precipitate was settled at the bottom. 30 ml water was added and slurry heated to 85 $^{\circ}C$ and filtered hot. The orange precipitate obtained on filtration was again treated with 20 ml glacial acetic acid, heated to 85 $^{\circ}C$ and filtered hot. The residue discarded and to the combined filtrates were added sufficient ammonia with continuous stirring to a pH-6. The crude product was obtained as a yellow precipitate, which was filtered and washed thoroughly with cold water (50 ml). The crude product was recrystallized with ethanol and water [9] [10].

**Synthesis of 2-hydrazino-7-chloro-6-fluoro benzothiazole (3):**
Hydrazine hydrate (5 ml) was placed in a 100 ml 3 necked RBF fitted with mechanical stirrer, addition funnel and a thermometer and cooled to 5 $^{\circ}C$ using an ice bath. To this was added conc.HCl (5 ml) followed by ethylene glycol (20 ml) with continuous stirring, maintaining the temperature between 5-10 $^{\circ}C$. 2-amino-7-chloro-6–fluorobenzothiazole **(2)** from step 1(2g, 9.90mmol) was added in 4-5 portions with gap of 2 min between each addition and with continuous stirring [11]. The addition funnel was replaced by a condenser and the reaction refluxed for 4h and periodically monitored by TLC for completion of the reaction. To the above reaction mixture add alcohol, ice cold water and cool it, filter through whatmann filter paper. Hygroscopic crystals appear allow them to form liquid [12] [13].

**Synthesis of 7-cholro-2-(3, 5-dimethyl-pyrazol-1-yl)-6-fluoro-benzothiazole (5):**
In a 100 ml 2 necked RBF fitted with a condenser were placed 2-hydrazino-7-chloro-6-fluorobenzothiazole **(3)** (liquid from second step), acetyl acetone (0.5ml, 0.005 mol) and 50 ml of ethanol. The reaction mixture was refluxed for 10h and periodically monitored by TLC for completion of the reaction. The reaction mixture was concentrated on hot plate to evaporate solvent ethanol and it was extracted with ethyl acetate. The ethyl acetate layer was collected into beaker which contains product (5). The ethyl acetate layer in the beaker was evaporated to obtain the product (5) and the product was purified with toluene (soluble solvent) & petroleum benzine (insoluble solvent) as it follows anti-solvent system mechanism to obtain pure product [14] [15].

**Substitution on 7-cholro-2-(3, 5-dimethyl-pyrazol-1-yl)-6-fluoro-benzothiazole by different groups: 6(a-k)**
In a dry 50 ml RBF fitted with a condenser was placed (**5)** (3.55 mmol) obtained in previous step. To this was added 10 ml of dry solvent (DMF), 3 to 4 equivalents of anhydrous potassium carbonate, 1.2-1.5 equivalents of the phenol/alcohol/amine. The reaction mixture was refluxed for 16–36h. Monitoring of the reaction was done by TLC with due care taken not to allow atmospheric oxygen into the reaction flask during sampling. After the completion of reaction, the mixture was cooled and poured into 100 ml of ice water, extracted with 3X20 ml portions of ethyl acetate. The combined organic layer was dried over anhydrous sodium sulphate and evaporated in vacuum to obtain the desired product. The crude product obtained was purified using toluene and petroleum benzine (anti-solvent system) [16] [17].




**Scheme 1**

***ANTIBACTERIAL ACTIVITY:***
**Study of antibacterial activity by agar diffusion method:**
Applying the agar plate diffusion technique all of the newly synthesized compounds were screened in vitro for antibacterial activity against ***Escherichia coli*** (Gram negative), ***Staphylococcus aureus*** (Gram-positive) at 75 µg/ml, 100 µg/ml, concentrations, respectively. Under identical conditions, the antibiotics Amoxicillin at 75 µg/ml, showed zone of inhibition 20 mm for Gram negative organism and showed zone of inhibition 22 mm at concentrations 100 µg/ml respectively for Gram positive organism [18] [19].

## RESULTS AND DISCUSSION

**Spectral data:**
**3-chloro-4-fluoroaniline (1):**
Black powder; mp, 45 $^{\circ}$C, IR ($\upsilon_{max}$, cm$^{-1}$, KBr): 790, 820 (C – Cl *str*), 1200 (C – F *str*), 1620 (N – H *def*), 1500 (C = C *str)*, 3450 (N – H *str*).

**2-amino-7-chloro-6-fluoro benzothiazole (2):**
Yield 76%; slight yellowish crystalline; mp, 180-182 $^{\circ}$C; IR ($\upsilon_{max}$, cm$^{-1}$, KBr): 736 (C – Cl *str*), 1261 (C – F *str*), 1617 (N – H *def*), 1527 (C = C *str)*, 2924 (C – H *str*), 3363 & 3441 (N – H *str*).

**2-hydrazino-7-chloro-6-fluoro benzothiazole (3):**
Yield 72%; white solid; mp, 256 $^{\circ}$C; IR ($\upsilon_{max}$, cm$^{-1}$, KBr): 862 (C – Cl *str*), 1201 (C – F *str*), 1619 (N – H *def*), 1475 & 1551 (C = C *str)*, 2962 (C – H *str*), 3317 (N – H *str*).

**7-cholro-2-(3,5-dimethyl-pyrazol-1-yl)-6-fluoro-benzothiazole(5):**
Yield 80.5%; white paper texture solid; mp, 167 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 827 (C – Cl *str*), 1203 (C – F *str*), 1649 (N – H *def*), 1450 & 1546(C = C).

**7-cholro-2-(3,5-dimethyl-pyrazol-1-yl)-6-fluoro-benzothiazole(5**):
**$^1$H NMR ($CDCl_3$) δ:** 2.30(s, 3H, $CH_3$ at 3), 2.74 (s, 3H, $CH_3$ at 5), 6.05(s, 1H, ArH), 7.55-7.59(d, 1H, ArH, J=8.28Hz), 7.87-7.90(d, 1H, ArH, J=6.53Hz)

**3-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-fluorobenzo(d)thiazol-7-yloxy)phenol (6a):**
Yield 75%; Brown color solid; mp, 85 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1147 (C – F *str*), 1460 (C = C), 2926 (C – H *str*), 3342(N – H *str*), 1166 ( C–O *str*), 3329 (O–H *str*).

**7-Benzyloxy-2-(3,5-dimethyl-pyrazol-1-yl)-6-fluoro-benzothiazole (6b):**
Yield 62%; Reddish brown solid; mp, 280 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1212 (C – F *str*), 1450 (C = C), 1637 (N – H *def*), 3416(C – H *str*), 1103 (C–O *str*).

**(2S)-2-amino-3-(4-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-6-fluorobenzo[d]thiazol-7-yloxy)phenyl)propanoic acid (6c):**
Yield 55%; light brownish color solid; mp, 265 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1132 (C – F *str*), 1450 (C = C), 1656 (N – H *def*), 2926 (C – H *str*), 995 (C–O *str*), 1114 (O–H *def*), 1656(C=O *str*), 3242(O–H *str*), 3547(N–H *str*).

**2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-fluoro-7-(2methoxyethoxy) benzo(d)thiazole (6d):**
Yield 50%; white color solid; mp, 200 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1229 (C – F *str*), 1452&1579 (C = C), 1604(N – H *def*), 2955 (C – H *str*), 1367 (C–O *str*).

**4-(2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-fluorobenzo(d)thiazol-7-yloxy)-2-methoxybenzaldehyde (6e):**
Yield 65%; slight brownish solid; mp, 250 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1251 (C – F *str*), 1452 (C = C), 1620 (N – H *def*), 2928 & 2980 (C – H *str aldehyde*), 1260 (C–O *str*), 1620 (C=O *str*), 3416 (C–H *aromatic).*

**2-(3,5-Dimethyl-pyrazol-1-yl)-6-fluoro-7-(Tri Ethanol amine)-benzothiazole (6f):**
Yield 72%; Black color solid; mp, 100 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1165 (C – O *str*), 1246 (C – F *str*), 1562 (C = C), 1639 (N – H *def*), 2956 (C – H *str*), 3377 (O–H *str*), 1072 (C–N *str).*

**2-(3,5-Dimethyl-pyrazol-1-yl)-6-fluoro-7-(4-methyl-piperazin-1-yl)-benzothiazole (6g):**
Yield 40%; Dark reddish brown solid; mp, 220 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1250 (C – F *str*), 1452 (C = C), 1649 (N – H *def*), 3090 (C – H *str*), 1156 (C–N *str*).

**2-(3,5-Dimethyl-1H-pyrazol-1-yl)-N,N-diethyl-6-fluorobenzo(d)thiazol-7-amine (6h):**
Yield 46%; Black color solid; mp, 235 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1217 (C – F *str*), 1450 & 1546 (C = C), 1649 (N – H *def*), 3091 (C – H *str*), 3404 (C–N *str*).

**2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-fluoro-7-(piperidin-1-yl)benzo(d)thiazole (6i):**
Yield 55%; Brown solid; mp, 190 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1217 (C – F *str*), 1458 & 1546 (C = C), 1644 (N – H *def*), 3081 (C – H *str*), 1189 (C–N *str*).

**2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-fluoro-7-(pyrrolidin-1-yl)benzo(d)thiazole (6j):**
Yield 62%; Black solid; mp, 178 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1267 (C – F *str*), 1448 & 1546 (C = C), 1610 (N – H *def*), 2972 (C – H *str*), 1172 (C–N *str*).

**2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-fluoro-7-(piperazin-1-yl)benzo(d)thiazole (6k):**
Yield 56%; Slight grey color solid; mp, 255 °C; IR ($\upsilon_{max}$, $cm^{-1}$, KBr): 1207 (C – F *str*), 1450 & 1618 (C = C), 1637 (N – H *def*), 3238 (C – H *str*), 3414 (C–N *str*).

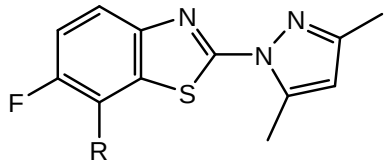
## DISCUSSION

The 2-amino-7-chloro-6-flouro benzothiazole **(2)** was successfully synthesized by reacting 4-fluoro-3-chloroaniline **(1)** with Potassium thiocyanate in presence of bromine in glacial acetic acid **(scheme 1).** Its formation was qualitatively determined by TLC using ninhydrin reagent and Ehrlich reagent, dyeing reagents for the detection of the amino group. IR spectrum showed its characteristic peak at 1527 $cm^{-1}$ due to Ar C=C, 2924 $cm^{-1}$ due to C-H, 1261 $cm^{-1}$ due to C-F, 3441, 3363 $cm^{-1}$ due to $NH_2$ str, 736 $cm^{-1}$ due to C-Cl which conformed the formation of compound **2.** This on further treatment with hydrazine hydrate yielded 2-hydrazino- 7-chloro-6-fluoro benzothiazole **(3)**. The formation of compound **3** was indicated by ninhydrin reagent and its IR spectra. The IR spectrum showed peak at 862 $cm^{-1}$ due to C – Cl str, 1201 $cm^{-1}$ due to C – F str, 1619 $cm^{-1}$ due to N – H *def*, 1475 & 1551 $cm^{-1}$ due to C = C *str*, 3317 $cm^{-1}$ due to N – H str, 2962 $cm^{-1}$ due to $CH_3$ str**.** 7-Chloro-2-(3,5-dimethyl-pyrrazol-1-yl)-6-fluoro benzothiazole **(5)** was synthesized by cyclization of compound **(3)** with acetyl acetone**(4) (scheme 1).** The IR spectrum showed its characteristic peak at 827 $cm^{-1}$ due to C – Cl, 1203 $cm^{-1}$ due to C – F, 1649 $cm^{-1}$ due to N – H *def*, 1450 & 1546$cm^{-1}$ due to aromatic C = C. The $^1$H NMR spectrum of this compound has been showed its characteristic peak at 7.87-7.90 (d, 1H, Ar-H, J=6.53 Hz), 7.55-7.59 (d, 1H, Ar-H, J=8.28 Hz), 6.05 (s, 1H, Ar-H), 2.74 (s, 3H, $CH_3$ at 5$^{th}$ position), 2.30 (s, 3H, $CH_3$ at 3$^{rd}$ position). All these data clearly indicated the formation of compound (**5).**

The final derivatives were obtained by replacing chlorine via a nucleophilic substitution reaction with various amines and alcohols. Use of $K_2CO_3$ and DMF was critical to improve the yield of the reaction. It was also observed that reaction time considerably reduced. The absence of C-Cl frequencies in the IR spectra has clearly indicated that replacement of the chlorine. Physicochemical properties of the new compounds have shown in **Table No.1**.

**Table No. 1: Physicochemical properties**

**General structure**




| S. NO. | C.C. | | Molecular Formula | M.wt. | M.P (°C) | $R_f$ Value | Sol. sys |
|---|---|---|---|---|---|---|---|
| **1.** | 6a | -Resorcinol | $C_{18}H_{14}FN_3O_2S$ | 355.39 | 85 | 0.76 | n-HEX:EA 1:1 |
| **2.** | 6b | -Benzyl alcohol | $C_{19}H_{16}FN_3OS$ | 353.41 | 280 | 0.68 | n-HEX:EA 1:1 |
| **3.** | 6c | -L-Tyrosine | $C_{21}H_{19}FN_4O_3S$ | 426.46 | 265 | 0.71 | n-HEX:EA 1:1 |
| **4.** | 6d | -2-Methoxy ethanol | $C_{15}H_{16}FN_3O_2S$ | 321.37 | 200 | 0.48 | n-HEX:EA 1:1 |
| **5.** | 6e | -Vanillin | $C_{20}H_{16}FN_3O_3S$ | 397.42 | 250 | 0.75 | n-HEX:EA 1:1 |
| **6.** | 6f | -Triethanol amine | $C_{18}H_{23}FN_4O_3S$ | 394.46 | 100 | 0.52 | n-HEX:EA 1:1 |
| **7.** | 6g | -N-Methyl Piperazine | $C_{17}H_{20}FN_5S$ | 345.44 | 220 | 0.40 | n-HEX:EA 1:1 |
| **8.** | 6h | -Diethyl amine | $C_{16}H_{19}FN_4S$ | 318.41 | 235 | 0.75 | n-HEX:EA 1:1 |
| **9.** | 6i | -Piperidine | $C_{17}H_{19}FN_4S$ | 330.42 | 190 | 0.82 | n-HEX:EA 1:1 |
| **10.** | 6j | -Pyrrolidine | $C_{16}H_{17}FN_4S$ | 316.40 | 178 | 0.88 | n-HEX:EA 1:1 |
| **11** | 6k | -Piperazine | $C_{16}H_{18}FN_5S$ | 331.41 | 255 | 0.50 | n-HEX:EA 1:1 |

**Anti-bacterial evaluation:**

All the tested compounds showed weak to moderate anti-bacterial activity by agar diffusion method **(Table No. 2)**. Best result in terms of anti-bacterial activity, were shown by **6(g)**, **6(k)** and 6**(f)** which have N-methyl Piperazine, Piperazine, Triethanol amine moieties substitution on 7$^{th}$ position of 7-Chloro-2-(3,5-dimethyl-pyrrazol-1-yl)-6-fluorobenzothiazole.

**Table No. 2 ANTI-BACTERIAL ACTIVITY**

| Sl. No. | Comp. Code | Zone of Inhibition (Diameter in mm) *Staphylococcus aureus* (+ve) 100 µg/ml | *Bacillus subtillis* (-ve) 75 µg/ml |
|---|---|---|---|
| 1 | 6a | 12 mm | 06mm |
| 2 | 6b | 08 mm | NA mm |
| 3 | 6c | 06 mm | 05 mm |
| 4 | 6d | NA | NA mm |
| 5 | 6e | 09 mm | 07 mm |
| **6** | **6f** | 13 mm | 10 mm |
| **7** | **6g** | 16 mm | 12 mm |
| **8** | **6h** | 08 mm | NA |
| **9** | **6i** | 10 mm | 09 mm |
| **10** | **6j** | 13 mm | 10 mm |
| **11** | **6k** | 14 mm | 11 mm |
| **Amoxicillin** | | 22 mm | 20 mm |

## CONCLUSION

The purpose of the present work was to synthesize, characterize and evaluate the biological activity of 7 substituted 2-(3,5-dimethyl-pyrrazol-1-yl)-6-fluorobenzothiazole **6 (a-k)** derivatives. In the present work eleven novels successfully synthesized derivatives characterized by various physicochemical and spectral techniques. All the synthesized compounds were subjected to anti-bacterial evaluation.

Best result in terms of anti-bacterial activity, were shown by **6(g)**, **6(k)** and 6**(f)** which have N-methyl Piperazine, Piperazine, Triethanol amine moieties substitution on 7$^{th}$ position of 7-Chloro-2-(3,5-dimethyl-pyrrazol-1-yl)-6-fluorobenzothiazole. Hence 7-Chloro-2-(3,5-dimethyl-pyrrazol-1-yl)-6-fluorobenzothiazole derivatives can be good lead molecules for the investigation as anti-bacterial agents.

Further lead optimization should be carried out for the better anti-bacterial activity.

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