Synthesis of organic salts from 1,10-phenanthroline for biological applications
Atakilt Abebe1*, Minaleshewa Atlabachew1, Misganaw Liyew2 and Elsabet Ferede2

Abstract: Molecular 1,10-phenanthroline has superb intercalation ability with DNA base pairs. However, it could not be used for medicinal applications. This is due to its toxicity caused by inhibiting metalloenzymes via its chelating nitrogen atoms. Nonetheless, the toxicity has been avoided for its attractive features coordinating with transition metals. However, this required lengthy synthetic work and rendering the final application is more laborious, expensive and less environmentally friendly. Moreover, this usually results in rigid three-dimensional complexes that prevents the complete intercalation of the coordinated 1,10-phenanthroline with DNA base pairs which diminishes its activity. In this work, an alternative strategy in diminishing the toxicity but retaining the flat geometry of 1,10-phenanthroline following simpler synthetic procedure without the involvement of transition metals is described. This was achieved synthesizing five N-alkyl-1,10-phenanthroline bromide salts. The salts were characterized by spectrometry (1H NMR, ESI MS, Uv-vis), CHNBr elemental analysis and conductivity measurements. All demonstrated amphiphilic property, which make their applications convenient. Their in vitro biological activities were tested on two Gram-positive (Staphylococcus aureus (S. aureus) and Streptococcus pyogens (S. pyogenes)) and two Gram-negative (Eschericia coli (E. coli) and Klebsiella pneumoniae (K. pneumoniae)) bacteria and compared with 1,10-phenanthroline. They are found active against all the tested bacteria. The minimum inhibitory concentrations of the salts are nearly the same as 1,10-phenanthroline. The increase in
the alkyl chain length increased the antibacterial activities of the slats in all the tested bacteria. All the salts demonstrated high molar conductivities.

Subjects: Microbiology; Biotechnology; Medicinal & Pharmaceutical Chemistry; Organic Chemistry; Applied & Industrial Chemistry; Inorganic Chemistry; Complementary & Alternative Medicine

Keywords: 1, 10-phenanthroline; N-alkyl-1; 10-phenanthrolinium; intercalation; antibacterial; alkyl chain length; amphiphilic

1. Introduction
Numerous biological experiments have demonstrated that DNA is the primary intracellular target of different drugs (Eriksson, Leijon, Hiort, Norden, & Graeslund, 1994; Lying, Rodger, & Nordén, 1991; Lyng, Rodger, & Nordén, 1992). This is because the interaction of molecules of the drug with DNA results in damage in cancer and other pathogen cells. The later blocks cell division and results in cell death (Dasari & Tchounwou, 2014; Hemmert et al., 2001; Li et al., 1996).

Therefore, identification and/or designing of compounds with the potential to interact with DNA have been the major concern of many researchers (Abdel and Baker, 2017; Ma, Chan, Lee, Kwan, & Leung, 2011; Sheng, Gan, & Huang, 2013). Aromatic molecules with rigid planar or approximately planar aromatic ring structure systems having stacking interaction ability with DNA base pairs are the primary choices (El-Kalyoubi, Fayed, & Abdel-Razek, 2017; Tawani, Amanullah, Mishra, & Kumar, 2016; Yadav et al., 2017; Zimmerman, 1991). 1,10-Phenanthroline is endowed with the later qualities. The conveniently placed nitrogen atoms, rigid planar structure, electron-poor heteroaromatic and \( \pi \)-acidic properties synergistically made 1,10-phenanthroline a classic chelating bidentate ligand (Abebe & Hailemariam, 2016; Ng et al., 2008). This makes it aggressively toxic compound expressed, for instance, by removing metal ions required for catalysis and inhibiting metalloenzymes (Newton, Ko, Ta, Av-Gay, & Fahey, 2006; Steffek, Newton, Av-Gay, & Fahey, 2003). Recognizing this, Dawyer et al. made an investigation on the biological activities of hydrochloride and methyl iodide as well as ethyl iodide quaternary salt forms of 1,10-phenanthroline (Dwyer, Reid, Shulman, Laycock, & Dixson, 1969). The purposes of protonation and quaternization were to destroy the chelating property, so that the toxicity by metal removal from metalloenzymes is prevented. The result showed the biological activities of the three salts to be similar. Extending their investigation, Dwyer et al. compared the activities of hydrochloride and methyl iodide as well as ethyl iodide quaternary salts of 1,10-phenanthroline substituted with electron donating and electron withdrawing groups. Nevertheless, similar results as above were obtained (Dwyer et al., 1969). Researches in the field of pharmacological applications resumed to make use of favorable properties of 1,10-phenanthroline by coordinating with transition metal ions (Cusumano, Di Pietro, & Giannetto, 2006; Gup & Kirkan, 2006; Turel et al., 2015). The primary purpose of this activity is for the fine-tuning the properties of the metal ion to penetrate into the lipid membrane (Shulman, Cade, Dumble, & Laycock, 1972). This enables the complex to disrupt the normal activities of the bacteria binding with DNA via a multitude of interactions (Lakshmi, 2009). While coordinating, the properties of 1,10-phenanthroline are also modified (Lawrence, 2010). The coordination with transition metal ions eliminates its enzyme inhibition properties. This is because the nitrogen atoms involved in denaturing metalloenzymes are engaged for coordination. Several researchers synthesized a large number of coordination compounds of 1,10-phenanthroline with many transition metal ions which demonstrated features such as probes of nucleic acid structures (Sigman, Landgraf, Perrin, & Pearson, 1996), chemical nuclease (Feeney, Kelly, Tossi, Kirsch-De Mesmaeker, & Lecomte, 1994; Perrin, Mazumder, & Sigman, 1996), fluorescence probes (Xu, Yang, Mallouk, & Bard, 1994), and electron transfer systems (Arkin et al., 1996; Barton, 1986). Nevertheless, the rigid and non-flat structures of the coordination compound formed prevents the complete intercalation of 1,10-phenanthroline to the base pairs of DNA strand (Satyanarayana, Dobrowiak, & Chaires, 1993, 1992). This is believed to diminish the efficiency of the complexes.
The current study furthers the investigation attempts of Dwyer et al. by synthesizing unsubstituted quaternary \( \text{N-alkyl-1,10-phenanthrolinium salt} \) employing alkylbromides with fairly longer alkyl chain length of five, six, eight, ten and twelve carbons. This results in an amphiphilic, serpentine-like, flat head cation. The amphiphilicity is a consequence of the combined effects of the lipophilic alkyl chain and the hydrophilic positively charged aromatic ring portion (Bonchio et al., 2012; Villar-Garcia, Abebe, & Chebude, 2012). Unlike Dwyer et al., we used longer alkyl chain with the intention of increasing the lipophilicity at the same time decreasing the polarity of the quaternary salt so that its penetration into the cell lipid membrane increases. Consequently, its biological activity increases better than those with short alkyl chain. This activity significantly distinguishes the current study. Comparative biological activities among quaternary salts as well as with molecular 1,10-phenanthroline are made and the influence of the alkyl chain on the biological activities is observed.

The purpose of our investigation is to encourage an alternative approach to the use of 1,10-phenanthroline coordinated with transition metal ions avoiding the risk of denaturing metalloenzymes and retaining its attractive flat structure. This possibly results in a complete intercalation in both the major and minor grooves of DNA.

2. Experimental section

2.1. Materials and methods

All chemicals used in the present work, viz., 1,10-phenanthroline, 1-bromoalkanes, 1,4-dioxane, are all from Sigma-Aldrich and are used as received.

The structures of the prepared compounds were confirmed by their \( ^1\)H NMR, using a Bruker AM-270 (270 MHz) spectrometer dissolving in dueterated dimethylsulfoxide, acetone, and chloroform. ESI MS was obtained using Bruker MicroTOF for the cation. The absorption wavelength in the UV-vis was recorded using Cary 60, version 2.00 in the range 800–200 nm, UV-vis scan rate 600 nm/min taking 0.01 mM solution. CHN elemental analysis was done using 5E-CHN2200 Elemental Analyzer taking 15 mg sample. Bromide estimation was conducted taking 100 mg sample dissolved in 40 mL distilled water. Excess AgNO \(_3\) solution was added for the formation of silver bromide (AgBr) precipitate. Then the cruddy white precipitate formed was filtered, dried in an oven and the amount of bromide was calculated from the weight difference. Their conductivity for \( 10^{-3} \) M solution in deionized water was also recorded at 298 K.

2.2. Synthesis

1,10-Phenanthroline monohydrate was heated in an oven at 105°C for 2 h to generate the anhydrate. To 2.00 g (11.1 mmol) 1,10-phenanthroline dissolved in dried 1,4-dioxane in a 100 ml two-necked round-bottomed flask fitted to reflux condenser and guarded from moisture using CaCl\(_2\), being stirred in an oil bath, molar equivalent 1,4-dioxane solution of 1-bromoalkane were added from a dropping funnel. The optimization of duration of stirring and temperature was made using tin layer chromatography follow-up. The product yields and optimization reaction conditions are summarized in Table 1.

In all cases, gray precipitate products were obtained. The precipitates were filtered and \([\text{C}_5\text{H}_{11}\text{Phen}]\text{Br}\) and \([\text{C}_6\text{H}_{13}\text{Phen}]\text{Br}\) were washed thoroughly with acetone while \([\text{C}_8\text{H}_{17}\text{Phen}]\text{Br}\), \([\text{C}_{10}\text{H}_{21}\text{Phen}]\text{Br}\), and \([\text{C}_{12}\text{H}_{25}\text{Phen}]\text{Br}\) (which are soluble in acetone) were washed with 1,4-dioxane three times each. The synthesis strategy is indicated in Scheme 1.

\( ^1\)H NMR spectra

The chemical shift and multiplicity data of the \( ^1\)H NMR of the compounds are indicated as follows. [\( \text{C}_7\text{H}_{15}\text{N}_2\text{Br} \); \( ^1\)H NMR (100 MHz, Chloroform-d6)] \( \delta \) ppm: 0.88 (s, 3 H) 1.31–1.51 (m, 2 H) 1.50–1.69 (m, 2 H) 2.12 (s, 2 H) 6.12–6.36 (m, 2 H) 7.93 (dt, J = 2.16, 1.18 Hz, 1 H) 8.20–8.35 (m, 1 H)
8.40 (s, 1 H) 8.48–8.57 (m, 1 H) 8.62 (s, 1 H) 9.23 (s, 1 H) 9.48 (s, 1 H) 10.40 (s, 1 H) (Figure 1a), [C_{18}H_{21}N_{2}]Br: ¹H NMR (270 MHz, DMSO-d6) δ ppm 0.75–1.02 (m, 3 H) 1.20–1.46 (m, 4 H) 1.54 (quin, J = 7.09 Hz, 2 H) 2.06 (quin, J = 7.57 Hz, 2 H) 5.77–5.99 (m, 2 H) 8.07 (dd, J = 8.13, 4.27 Hz, 1 H) 8.30–8.56 (m, 3 H) 8.80 (dd, J = 8.26, 1.79 Hz, 1 H) 9.31 (dd, J = 4.27, 1.79 Hz, 1 H) 9.40 (dd, J = 8.19, 1.31 Hz, 1 H) 9.62 (dd, J = 5.92, 1.38 Hz, 1 H) (Figure 1b), [C_{20}H_{25}N_{2}]Br: ¹H NMR (270 MHz, DMSO-d6) δ ppm 0.85 (s, 3 H) 1.26 (br. s., 8 H) 1.53 (br. s., 2 H) 2.06 (br. s., 2 H) 5.90 (br. s., 2 H) 8.08 (s, 1 H) 8.41 (s, 3 H) 8.79 (s, 1 H) 9.31 (s, 1 H) 9.40 (dd, J = 8.19, 1.31 Hz, 1 H) 9.61 (s, 1 H) (Figure 1c), [C_{22}H_{29}N_{2}]Br: ¹H NMR (270 MHz, DMSO-d6) δ ppm −0.06–0.11 (m, 3 H) 0.28–0.71 (m, 17 H) 0.74–0.91 (m, 2 H) 1.34–1.52 (m, 2 H) 5.17–5.46 (m, 2 H) 7.27 (dd, J = 8.26, 4.27 Hz, 1 H) 7.49–7.74 (m, 3 H) 7.99 (dd, J = 8.26, 1.79 Hz, 1 H) 8.44–8.72 (m, 2 H) 8.83 (dd, J = 5.92, 1.51 Hz, 1 H) (Figure 1d), [C_{24}H_{33}N_{2}]Br: ¹H NMR (270 MHz, ACETONE-d6) δ ppm 0.86 (s, 3 H) 1.27 (br. s., 14 H) 1.46 (br. s., 2 H) 1.57–1.77 (m, 2 H) 2.27 (s, 2 H) 6.08–6.24 (m, 2 H) 8.11 (dd, J = 8.26, 4.27 Hz, 1 H) 8.39–8.58 (m, 3 H) 8.83 (dd, J = 8.26, 1.79 Hz, 1 H) 9.37–9.52 (m, 2 H) 9.67 (dd, J = 5.99, 1.45 Hz, 1 H) (Figure 1e).

Table 1. Optimization reaction conditions and reaction products yields

<table>
<thead>
<tr>
<th>Alkylhalide</th>
<th>Optimum temperature/°C</th>
<th>Duration/h</th>
<th>Yield/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-bromopentane/C_{5}H_{11}Br</td>
<td>30</td>
<td>6</td>
<td>3.56</td>
</tr>
<tr>
<td>1-bromohexane/C_{6}H_{13}Br</td>
<td>30</td>
<td>12</td>
<td>3.67</td>
</tr>
<tr>
<td>1-bromoctane/C_{8}H_{17}Br</td>
<td>35</td>
<td>18</td>
<td>3.84</td>
</tr>
<tr>
<td>1-bromoodecane/C_{10}H_{21}Br</td>
<td>40</td>
<td>24</td>
<td>4.00</td>
</tr>
<tr>
<td>1-bromododecane/ C_{12}H_{25}Br</td>
<td>45</td>
<td>36</td>
<td>4.10</td>
</tr>
</tbody>
</table>

Scheme 1. Synthesis path for the salts.

Figure 1. a-e: 1H NMR spectra of (a) [C_{17}H_{19}N_{2}]Br, (b) [C_{18}H_{21}N_{2}]Br, (c) [C_{20}H_{25}N_{2}]Br, (d) [C_{22}H_{29}N_{2}]Br, and (e) [C_{24}H_{33}N_{2}]Br.
2.3. Antibacterial activity testing

The organic salts were evaluated for in vitro antibacterial activities against strains of two Gram-positive (S. aureus (ATCC25923) and S. pyogenes) and two Gram-negative (E. coli (ATCC255922) and K. pneumoniae (ATCC986605) bacteria. The bacterial strains were maintained in the appropriate blood agar base at 4°C. Antibiotic discs (Gentamycin 10 μg) were used as reference. The minimum inhibitory concentration (MIC) against each bacterium was determined by preparing aqueous solutions of different concentrations of the salts by serial dilution (50 μg/mL, 100 μg/mL, 150 μg/mL, 200 μg/mL, 250 μg/mL, 300 μg/mL, 350 μg/mL, and 400 μg/mL). The experiments were repeated three times to obtain consistent results. The percent activity compared with the reference was also determined.

3. Results and discussions

The synthesized compounds are stable in air. They are soluble in water, methanol, ethanol, acetonitrile, and DMSO. C\textsubscript{17}H\textsubscript{29}N\textsubscript{2}Br and C\textsubscript{24}H\textsubscript{33}N\textsubscript{2}Br dissolve in acetone in addition. Elemental analyses of all the compounds were in agreement with the assigned formula (Table 2). They showed high molar conductivity values in water (Table 2). This is attributed to the high speed of mobility of the ions. This is a consequence of the presence of the hydrophobic alkyl chain and positive charge in the aromatic ring portion (Bonchio et al., 2012). The former reduces the drifting (counter directional) speed due to the interaction with the solvent cavity surrounding the cation (Atkins, 1994).

The reaction gives only a monoquaternary N-alkyl-1,10-phenanthroline bromide as a product. This is evident from the symmetry loss of 1,10-phenanthroline molecule after the quaternization. This new characteristic feature helps in the identification of the new salt, since a total of eight peaks appear in the aromatic region. Only four peaks would have appeared in that region in both diquaternization and non-quaternization. Moreover, the up field appearance of appropriate number of alkyl protons and the change in the chemical shift of aromatic protons are strong confirmations for the occurrence of quaternization (Figure 1). Diquaternization of 1,10-phenanthroline is not possible due to the steric hindrance resulted following the first quaternization (Summers, 1978).

3.1. Mass spectra

The ESI MS spectra of the salts were recorded and the obtained molecular ion peaks confirmed the acquisition of the expected salts with the proposed formulae. The mass spectra of \([C\textsubscript{18}H\textsubscript{21}N\textsubscript{2}]Br\), \([C\textsubscript{20}H\textsubscript{25}N\textsubscript{2}]Br\), \([C\textsubscript{22}H\textsubscript{29}N\textsubscript{2}]Br\), and \([C\textsubscript{24}H\textsubscript{33}N\textsubscript{2}]Br\) appeared at m/z 265, 293, 321 and 349 which corresponds to \([C\textsubscript{18}H\textsubscript{21}N\textsubscript{2}]^+\), \([C\textsubscript{20}H\textsubscript{25}N\textsubscript{2}]^+\), \([C\textsubscript{22}H\textsubscript{29}N\textsubscript{2}]^+\), and \([C\textsubscript{24}H\textsubscript{33}N\textsubscript{2}]^+\), respectively (Figure 2a-d, Table 2).

3.2. Uv-vis spectra

In order to study the electronic environment of the salts, the Uv-vis spectra of 1,10-phenanthroline was compared with the spectra of the salts (Figure 3). The Uv-vis spectrum of 1,10-phenanthroline
shows bands at 228 nm and 264 nm assignable to n→π* and π→π*, respectively. Following the quaternization, these bands appeared shifted to 222 nm and 271 nm, respectively. This is because, the quaternization involves the non-bonding electron in the bonding thereby lowering the energy. The later increases the energy gap between the non-bonding and the π* orbitals. On the other hand, the positive charge developed in the ring system inductively influences increasing the energy of the π orbitals. Subsequently, it decreases the energy gap between π and π* orbitals.

### 3.3. Antibacterial screening

The synthesized organic salts were tested for their in vitro antibacterial activity. They were tested against two Gram-positive (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two Gram-negative (*Eschericia coli* and *Klebsiella pneumoniae*) bacteria (Table 3, Figure 4). The MIC values of the salts are summarized in Table 4. Even though they are less active than 1,10-phenanthroline, all the salts are biologically active against all pathogens. This can be attributed, on the one hand, to the prevention of 1,10-phenanthroline from removing the essential metal ions, on the other, to the decrease in the stack-ability as the long alkyl chain increases the steric hindrance on the aromatic ring that coming closer to the DNA base pairs becomes difficult. Nonetheless, a direct relationship between the quaternizing alkyl chain length and activity of the salt is observed. This may be due to the increase in the aliphatic alkyl chain which increases the cell permeability as the lipid membrane that surrounds

### Table 2. CHNBr elemental analysis, ESI MS and conductance measurements values

<table>
<thead>
<tr>
<th>Compound</th>
<th>H</th>
<th>C</th>
<th>N</th>
<th>Br</th>
<th>m/z value</th>
<th>C_{r-n}Phen*</th>
<th>Molar conductivity, ( \Lambda_m ) (S cm(^{-2})mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>[C(<em>{17})H(</em>{19})N(_2)]Br</td>
<td>5.74 (5.72)</td>
<td>61.63 (61.62)</td>
<td>8.46 (8.40)</td>
<td>24.17 (23.99)</td>
<td>–</td>
<td>194.2</td>
<td></td>
</tr>
<tr>
<td>[C(<em>{18})H(</em>{21})N(_2)]Br</td>
<td>6.09 (6.05)</td>
<td>62.61 (62.58)</td>
<td>8.12 (8.07)</td>
<td>23.88 (23.81)</td>
<td>265</td>
<td>192.5</td>
<td></td>
</tr>
<tr>
<td>[C(<em>{20})H(</em>{25})N(_2)]Br</td>
<td>6.70 (5.98)</td>
<td>57.91 (57.87)</td>
<td>7.51 (7.38)</td>
<td>21.45 (21.36)</td>
<td>293</td>
<td>182.7</td>
<td></td>
</tr>
<tr>
<td>[C(<em>{22})H(</em>{29})N(_2)]Br</td>
<td>7.23 (7.22)</td>
<td>65.83 (65.80)</td>
<td>6.98 (6.91)</td>
<td>19.95 (19.52)</td>
<td>321</td>
<td>177.0</td>
<td></td>
</tr>
<tr>
<td>[C(<em>{24})H(</em>{33})N(_2)]Br</td>
<td>7.69 (7.66)</td>
<td>67.13 (67.09)</td>
<td>6.53 (6.42)</td>
<td>18.65 (18.24)</td>
<td>349</td>
<td>170.0</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Uv-vis spectra of 1, 10-phenanthroline and the salts.
the cell favors the passage of lipid-soluble materials. Therefore, liposolubility is an important factor for molecules to pass the cell wall and/or cell membrane reach to the target (Anjaneyulu & Rao, 1986).

4. Conclusions
All characterization techniques employed here confirmed the synthesis of the intended salts. The result of the in vitro biological activities studies indicated that all the salts are biologically active against all the tested pathogens. The activities of the salts are less than the starting molecular 1,10-phenanthroline. This is due to the engagement of one of the nitrogen atoms in the quaternization which was used in removing essential metal ions from the cell. Moreover, the reduced intercalation ability due to steric reasons following the alkylation might contributed to the decreased biological activity compared to 1,10-phenanthroline. Even though less active than 1,10-phenanthroline, the activity of the salts increases with increase in the quaternizing aliphatic alkyl chain length. This may indicate that the increase in the penetration of the salts in to the cell through the cell wall and/or cell membrane is a function of the lipid-soluble materials. Thus, after

<table>
<thead>
<tr>
<th>Compound</th>
<th>Gram-negative bacteria</th>
<th>Gram-positive bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
<td>K. pneumoniae</td>
</tr>
<tr>
<td>1,10-Phenanthroline</td>
<td>32.75 ± 0.12</td>
<td>21.88 ± 0.13</td>
</tr>
<tr>
<td>[C17H19N2]Br</td>
<td>10.93 ± 0.31</td>
<td>7.75 ± 0.23</td>
</tr>
<tr>
<td>[C18H21N2]Br</td>
<td>11.83 ± 0.22</td>
<td>10.25 ± 0.23</td>
</tr>
<tr>
<td>[C20H25N2]Br</td>
<td>14.00 ± 0.01</td>
<td>12.50 ± 0.14</td>
</tr>
<tr>
<td>[C22H29N2]Br</td>
<td>20.25 ± 0.24</td>
<td>14.00 ± 0.23</td>
</tr>
<tr>
<td>[C24H33N2]Br</td>
<td>22.50 ± 0.20</td>
<td>14.00 ± 0.10</td>
</tr>
</tbody>
</table>

Figure 4. The inhibition observed by the actions of 1, 10-phenanthroline and the salts on Gram-positive bacteria (S. aureus and S. pyogenes) and Gram-negative bacteria (E. coli and K. pneumoniae).
cytotoxicity investigations, the possible use of these salts to transport 1,10-phenanthroline for intercalation to the DNA of the cells as an alternative to its metal complexes can be considered. This minimizes the concern of introducing metal ions into the organism.

Competing interests
The authors declare no competing interest.

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References
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Table 4. MIC assays of the salts against the four bacterial pathogens

<table>
<thead>
<tr>
<th>Compound</th>
<th>Gram-negative bacteria</th>
<th>Gram-positive bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>K. pneumonia</td>
<td>S. aureus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. pyogenes</td>
</tr>
<tr>
<td>1,10-Phenanthroline</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>[C17H16N2]Br</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>[C18H17N2]Br</td>
<td>150</td>
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</tr>
<tr>
<td>[C24H24N4]Br</td>
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Minimum concentration of microorganism growth (µg/mL)


