PART –II

β-Cyclodextrin Catalyzed Cyclocondensations
Abstract

Part II is composed of two sections, Section-A and Section-B. These sections deal with the newly developed synthetic protocols for obtaining the molecules of interest viz. 2-aryl benzothiazoles and 1,4-benzothiazines under supramolecular catalysis of β-cyclodextrin in water.

Here β-cyclodextrin is used as biomimetic catalyst which catalyzes the cyclocondensations in water at ambient temperature and neutral pH. The catalytic role of the β-cyclodextrin in catalyzing the cyclocondensations has also been explained.
SECTION-A

Synthesis of 2-arylbenzothiazoles, catalyzed by biomimetic catalyst; β-cyclodextrin
**Introduction**

Benzothiazole and its derivatives are the most important heterocyclic molecules, which are common and integral feature of a variety of natural products and medicaments. Benzothiazoles show a variety of pharmacological properties and its analogs offer a high degree of structural diversity that has proven useful for the search of new therapeutic agents. The wide range of pharmacological activities of benzothiazole derivatives indicates that, this family of compounds is of an enormous interest.\(^1\) The related research and developments in benzothiazole-based medicinal chemistry have become a rapidly developing and increasingly active area day by day.

Structural modifications of benzothiazole nucleus yielded number of molecules having therapeutic importance. In the last decade there has been some interesting development in the synthesis as well as testing biological activities of benzothiazole derivatives. These compounds enjoy special significance in the field of medicinal chemistry due to their noteworthy pharmacological potentialities.\(^2\)

Benzothiazoles comprise a class of therapeutic compounds that show a wide range of biological activities\(^3\) such as anticancer,\(^4\) antimicrobial,\(^5\) anticonvulsant,\(^6\) antiviral,\(^7\) antitubercular,\(^8\) antimalarial,\(^9\) anthelmintic,\(^10\) analgesic,\(^11\) antiinflammatory,\(^12\) antidiabetic\(^13\) and fungicidal activities.\(^14\) Recently, benzothiazole derivatives have been evaluated as potential amyloid-binding diagnostic agents in neurodegenerative disease,\(^15\) selective fatty acid amide hydrolase inhibitors,\(^16\) inhibitors of stearoylcoenzyme A \(\delta-9\) desaturase,\(^17\) LTD4 receptor antagonist,\(^18\) orexin receptor antagonist 2,\(^19\) and histamine \(H_2\) antagonists.\(^20\) They are also useful as appetite depressants,\(^21\) intermediates for dyes,\(^22\) plant protectants,\(^23\) imaging agents for \(\beta\)-amyloid plaques,\(^24\) and photographic sensitizers.\(^25\)

Specifically 2-Substituted benzothiazole derivatives have emerged in its usage as a core structure in the diversified therapeutic applications. The studies of structure–activity relationship interestingly reveal that change of the structure of substituent group at C-2 position commonly results the change in its bioactivity. 2-Substituted benzothiazole derivatives constitute a large group of xenobiotics, which are synthesized worldwide for a variety of applications\(^26\) as shown in Fig. 2.1. The simplest member of the family, benzothiazole is a fungicide.\(^27\) Methabenzthiazuron (MBTU) is used as herbicide in winter corn crops and is an active ingredient of two
commercially available formula Tribunil and Ormet,28 slimicides in the paper and pulp industry.29 2-Aminobenzothiazole is used in the manufacture of some disperse azo dyes.30 Riluzole (2-amino-6-trifluoromethoxybenzothiazole) is marketed by Rhone-Poulenc (Rilutek) for treatment of amyotrophic lateral sclerosis31 and 2-(4-aminophenyl)benzothiazole evidenced antitumor properties.32 Benzothiazole derivatives catalyze the formation of sulfide linkages (reticulation) between unsaturated elastomeric polymers in order to obtain a flexible and elastic cross-linked material. 2-Mercaptobenzothiazole (MBT/ BTSH) is the main rubber accelerator used in certain specialty products and even in the tire production.33

![Fig. 2.1: Significance of benzothiazole derivatives](image)

Aminomethylphenyl, carbonitrile and bis amidino substituted 2-styryl benzothiazoles show selective growth inhibitory properties against human cancer cell lines,34 proliferation of cells35 and cytostasis36 respectively. Many chlorinated and fluorinated benzothiazole derivatives exhibit excellent in vitro as well as in vivo
antitumor activity. Fluorinated analogues of 2-(4-aminophenyl) benzothiazoles have been synthesized which successfully block C-oxidation.\(^{37}\) Fluorinated benzothiazole analogue, 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F203, NSC 703786) (\textbf{2.2}), exhibits selective potent anticancer activity.

![Image of Structure 2.2]

It is the favored analogue for clinical consideration possessing enhanced efficacy \textit{in vitro} and superior potencies against human breast and ovarian tumor xenografts implanted in mice. It’s lysylamide prodrug, (Phortress, NSC 710305), (\textbf{2.3}) is under phase I clinical trials in United Kingdom.

New 2-(1-piperazinyl)-benzothiazoles and 2-(hexahydro-1\(H\)-1,4-diazepin-1-yl) benzothiazoles (\textbf{2.4}) were prepared and tested as H1 and H3-receptor antagonists by Walczynski \textit{et al.},\(^{38}\)

![Image of Structure 2.3 and 2.4]

2-[3-Amino, 5-methylthio, 4-carboxamido pyrazol-1-yl] 6-fluoro, 7-chlorobenzothiazole was synthesized and screened for anthelmintic activity against \textit{P. posthuma} by Jayachandran \textit{et al.},\(^{39}\) The compound was found to possess remarkably higher anthelmintic activity.

Number of new 2-[(4-halophenyl) thioureido]-6-substituted benzothiazoles were synthesized by refluxing equimolar quantity of 2-amino-6-substituted benzothiazoles by Javed \textit{et al.}, The prepared compounds have been tested for their antibacterial activity against \textit{S. aureus} (Gram positive) and \textit{E. coli} (Gram negative) bacteria.\(^{40}\) Three new series of benzo[d]isothiazoles, benzothiazole and thiazole Schiff bases were synthesized by Vicini \textit{et al.} and these compounds were evaluated \textit{in vitro} against representatives of different virus classes, such as Retrovirus (HIV-1), a
Hepadnavirus (HBV), single-stranded RNA+ viruses, Yellow fever virus (YFV) and Bovine viral diarrhoea virus (BVDV).\textsuperscript{41}

Thioflavin T (2.5)\textsuperscript{42} (Basic Yellow 1 or CI 49005) is a benzothiazole salt obtained by the methylation of dehydrothiotoluidine with methanol in the presence of HCl. The dye is used to visualize plaques composed of amyloid beta found in the brains of Alzheimer's disease patients as well as other amyloid proteins.

Primuline (2.6)\textsuperscript{43} is a dye containing the benzothiazole ring system. It is a cotton dye of rather fugitive shade, but can be diazotized on the fiber and then developed with other components, yielding a series of ingrain colors.

The investigations of benzothiazole as a key pharmacophore led Merck to introduce new drugs such as the orexin receptor antagonist (2.7) and the Gram positive selective antibacterial (2.8).\textsuperscript{20,44}
(R)-CVT-3501 (2.9) shows excellent activity as a fatty acid oxidation inhibitor.\textsuperscript{45} Zopolrestat (2.10) has been used clinically for the treatment of diabetes.\textsuperscript{46,47}

A new thioamide derivative (2.11) of 8-hydroxyquinoline-benzothiazole was prepared and its fluorogenic chemodosimetric behavior toward transition metal ions has been investigated.\textsuperscript{48}

Recent successful examples include the anti-HIV agent (2.12),\textsuperscript{49} the antibacterial compound (2.13),\textsuperscript{50} the PPAR agonist (2.14),\textsuperscript{51} the H3-receptor ligand (2.15),\textsuperscript{52} the nicotinic-acetylcholine-receptor ligand (2.16),\textsuperscript{53} and the phosphodiesterase 10 inhibitor (2.17).\textsuperscript{54}
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Methods for the synthesis of benzothiazoles

The vast range of biological activities associated with this scaffold attracted the organic chemists to consider benzothiazole ring system as a privileged structure and to develop it’s convenient synthetic methodologies. There are number of methods reported in the literature for construction of this valuable added heterocyclic system. Following is a brief review on the methods, practiced for obtaining 2-aryl benzothiazoles.

1. Condensation of 2-aminothiophenols

The most widely used method involves the condensation of 2-aminothiophenols with substituted nitriles/ carboxylic acids/ aldehydes/ acyl chlorides or esters\(^56\) (Scheme 2.1). Number of catalysts, namely, (pmIm)Br,\(^57\) I\(_2\),\(^58\) ZrOCl\(_2\).8H\(_2\)O,\(^59\) TMSCl,\(^60\) H\(_2\)O,\(^61\) PCC,\(^62\) CAN,\(^63\) nano ceria (CeO\(_2\)),\(^64\) cyanide,\(^65\) boron trifluoride etherate,\(^66\) mesoporous CdS nanospheres,\(^67\) silica supported nano-
copper(II) oxide,\textsuperscript{68} baker’s yeast (whole-cell biocatalyst)\textsuperscript{69} and many more have been effectively used to prepare rapidly benzothiazole derivatives by this method.

![Scheme 2.1](image)

**Scheme 2.1**

2. Jacobson cyclization

Another familiar route known to prepare benzothiazoles is the Jacobson’s cyclization of thiobenzanilides.\textsuperscript{56,70} It is simple and effective method for synthesis of benzothiazole derivatives involving the cyclization (Scheme 2.2) of substituted thiobenzanilidines (in the presence of aqueous sodium hydroxide and potassium ferricyanide). But this route requires a multistep reaction sequence.\textsuperscript{71}

![Scheme 2.2](image)

**Scheme 2.2**

3. 2-Aryl benzothiazoles

a) Direct arylation at 2-position of benzothiazoles (Scheme 2.3) by employing various metal catalyst such as Pd (OAc)$_2$, NiBr$_2$, PXPd/Cu(Xantphos)I(dichlorobis(chloro-d-tert-butylphosphine)palladium, CuI/PPh$_3$ and copper oxide has also been reported.\textsuperscript{72-77}

![Scheme 2.3](image)

**Scheme 2.3**

b) **Suzuki coupling:** Palladium-catalyzed Suzuki biaryl coupling of 2-halobenzothiazoles with arylboronic acids is another method to obtain the 2-aryl benzothiazoles.\textsuperscript{78} (Scheme 2.4)
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Scheme 2.4

\[
\begin{align*}
\text{R}_1 \text{R}_2 \text{S} \text{X} + \text{HO-BORH} & \xrightarrow{\text{Pd}} \text{R}_1 \text{R}_2 \text{S} \text{R}_2 \\
\end{align*}
\]

Scheme 2.4

c) Tale reported the unique approach in which 2-aryl benzothiazoles were obtained by condensation of thiophenols with aromatic nitriles using ceric ammonium nitrate in acetonitrile. (Scheme 2.5).\(^{79}\)

\[
\begin{align*}
\text{SH} \text{R}_1 \text{R}_2 + \text{CN} \text{R}_3 \text{R}_4 & \xrightarrow{\text{CAN, NaHCO}_3} \text{R}_1 \text{R}_2 \text{S} \text{R}_3 \text{R}_4 \\
\end{align*}
\]

Scheme 2.5

d) Cyclization of \(o\)-halo bezothioanilides (Scheme 2.6), modification of Jacobsons cyclization has also been reported. This reaction is usually carried in a basic medium using copper salt and appropriate legands.\(^{80}\)

\[
\begin{align*}
\text{H} \text{N} \text{R}_1 \text{R}_2 \xrightarrow{\text{Cu Salt, legand}} \text{S} \text{R}_1 \text{R}_2 \\
\end{align*}
\]

Scheme 2.6

e) Recently the cross-coupling condensation of nitro-substituted aryl halides with benzylthiols using KOH and polyethylene glycol (Scheme 2.7) has been demonstrated to afford benzothiazole derivatives via a novel synthetic pathway. This condensation has been found to be completed within 2 h at room temperature.\(^{81}\)

\[
\begin{align*}
\text{NO}_2 \text{R}_1 \text{I} + \text{SH} \text{R}_2 \text{R}_1 \xrightarrow{\text{KOH, PEG 600}} \text{R}_1 \text{R}_2 \text{S} \text{R}_2 \\
\end{align*}
\]

Scheme 2.7
Scope and objectives

Many of these existing methods, used for the synthesis of benzothiazoles accompanying with one or other kind of the disadvantages, such as, use of volatile organic solvents, costly air sensitive reagents, prolonged reaction time, multistep reaction sequences, high reaction temperature, requirement of extreme pH, tedious work-up procedures and generation of solid wastes.\(^{69}\)

Recently, more efforts have been put on the use of biocatalysts i.e. functional enzymes as excellent catalysts\(^{82}\) to accelerate organic transformations because of their specificity and selectivity. Enzymes catalyze organic transformations at ambient temperature, atmospheric pressure and in an aqueous medium. These advantageous and distinguishing features of the enzymes have been utilized to carry out variety of organic transformations leading to bioactive molecules. There are number of reports appeared in the literature on enzymatic catalysis in organic synthesis.\(^{82}\) However, it is not always preferable to use the enzymes as a catalysts in the synthetic protocols, mainly due to the high cost of pure enzymes,\(^{83}\) solid waste management problems,\(^{69}\) less availability of pure enzymes, narrow substrate specificity and requirement of complicated co-substrates such as co-factors.\(^{84}\) Recently, we have reported the use of whole cell biocatalyst\(^{69}\) in the synthesis of benzothiazoles. There it was noticed that the route has been found to give good yields of the benzothiazoles but after prolonged reaction time. Further it requires huge amount of baker’s yeast as a catalyst. Therefore, this route has also problem of solid waste disposal and non-recyclibility of the biocatalyst.

To overcome these limitations and to retain the advantages of biocatalysts, readily available biomimetic catalysts are gaining more importance because of their selectivity, like enzymes and can be used at mild reaction conditions to run the chemical transformations leading to biodynamic molecules.\(^{85}\)

While revealing the literature it was observed that β-cycloexextrin, a biomimetic catalyst\(^{86}\) has been recently employed for carrying wide spectrum of organic transformations\(^{85}\) such as, synthesis of thiazoles, synthesis of β-hydroxy sulfides from alkenes, hydrolysis of oxiranes, deprotection of aromatic acetals, synthesis of selenazoles, Strecker reaction in water, regioselective ring opening of oxiranes with phenoxides, synthesis of quinoxalines in water etc. Bhosale et al. have
published a review which gives emphasis on the use of β-cyclodextrin as a catalyst in organic syntheses.\textsuperscript{87} It was also been revealed that, β-cyclodextrin does not find use in the cyclocondensation of aryl/heteraryl aldehydes and 2-amino thiophenol leading to 2-aryl/heteraryl benzothiazoles.

Considering all the above facts here objective was to develop an efficient and fast protocol for the cyclocondensation of 2-aminothiophenols and aryl/ heteroaryl aldehydes in aqueous medium under relatively mild reaction conditions using an easily available, cheaper supramolecular catalyst, β-cyclodextrin instead of the catalysts reported in the literature.\textsuperscript{57-69}

**Present work**

In the present work an efficient and cost effective synthetic protocol has been developed for obtaining 2-arylbenzothiazoles using milder reaction conditions. The condensation of 2-aminothiophenol and aryl/ heteroaryl aldehydes has been carried in water as a reaction medium, catalyzed by biomimetic catalyst, β-cyclodextrin at 50°C. (Scheme 2.8)

![Scheme 2.8](image)

**Results and discussion**

Considering the need of safer medium like water and importance of biomimetic (supramolecular) catalysts, we attempted the cyclocondensation of aryl aldehydes and 2-amino thiophenol, separately in cationic surfactant i.e. cetyltrimethyl ammonium bromide (CTAB), anionic surfactant sodium dodecyl sulphate (SDS) and non-ionic biomimetic catalyst, β-cyclodextrin (β-CD). It was observed that the condensation successfully led to benzothiazoles, when carried in aqueous β-cyclodextrin at 50 °C (Table 2.1).
Table 2.1: Optimization for selection of appropriate catalyst\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reaction Temperature (°C)</th>
<th>Time (h)</th>
<th>Yields (%)\textsuperscript{b}</th>
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<tr>
<td>1</td>
<td>aq. CTAB</td>
<td>50</td>
<td>9.5</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>aq. SDS</td>
<td>50</td>
<td>10</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>aq. β-CD</td>
<td>50</td>
<td>1.5</td>
<td>92</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 2-aminothiophenol (2 mmol), p-anisaldehyde (2 mmol), β-cyclodextrin (2 mmol) in water (40 ml). \textsuperscript{b}Isolated yields.

Encouraged by these observations we tried to optimize the reaction conditions to obtain better to excellent yields of the benzothiazoles using aqueous solution of β-cyclodextrin as a catalyst and medium. The condensation has been carried by varying amount of β-cyclodextrin and reaction temperature. It was noticed that better yields of the benzothiazoles were obtained when equimolar quantities of the alcoholic concentrated solutions of aldehydes and 2-aminothiophenol were stirred in equimolar aqueous solution (5.6%) of β-cyclodextrin at 50 °C. Here, rate enhancement of the cyclocondensations has been noted. The time required for the completion, compared to the condensation carried by baker’s yeast\textsuperscript{69} has been found to be markedly reduced from 24 hours to 2 to 3 hours. This protocol is superior as compared to the enzyme catalyzed cyclocondensation as it is not accompanying with solid waste and is relatively rapid and simple.

The rate acceleration of this condensation can be attributed to (1) aqueous β-cyclodextrin provides a unique hydrophobic truncated cone shaped cavity and hydrophilic outwardly hydroxyl groups. The aldehydes might be forming non covalent reversible supramolecular complexes (Scheme 2.9) with β-cyclodextrin in the cavity, enhancing the localized concentration of the aldehydes resulting in the dissolution of aldehydes in queous medium. Because of this aldehydes become readily available to interact with 2-aminothiophenol and (2) the electrophilic behavior of carbonyl carbon of the aldehydes would have been enhanced due to intermolecular hydrogen bonding between outwardly hydroxyl groups of β-cyclodextrin and carbonyl oxygen of the aldehydes. The enhancement in the localized concentration of aldehydes and electrophilic behavior of carbonyl carbon would be responsible to accelerate the condensation rate compared to the condensation carried by biocatalyst.
Syntheses of bioactive molecules, accelerated by biocatalysts/biomimics

Scheme 2.9: Plausible mechanism for the formation of benzothiazole

To generalize this biomimetic synthetic route (Scheme 2.8) for the synthesis of 2-substituted benzothiazoles, we have tried the reactions for a series of aromatic as well as hetero-aromatic aldehydes and 2-aminothiophenol for getting known as well as new benzothiazoles. As expected all the reactions proceeded smoothly to afford the desired products with good to excellent yields (Table 2.2).

In summary, an efficient and rapid supramolecular synthetic route is developed. The biomimetic role of β-cyclodextrin as a catalyst and possible mechanism responsible for rate acceleration of the present cyclocondensation is presented. The newly developed protocol has following advantages.

1) Use of water as medium makes the route green.

2) Reaction time is markedly reduced, making the route comparatively rapid.

3) β-cyclodextrin is recycled and reused, which makes the route economic.
Experimental section

General experimental procedure for the synthesis of 2-arylbenzothiazoles (3a-n):

β-Cyclodextrin (1 mmol) was dissolved in water (20 ml) with stirring at 50 °C. To this clear solution, alcoholic solution of aryl aldehydes (1 mmol in 2 ml ethanol) was added dropwise. To this then dropwise alcoholic solution of 2-aminothiophenol (1 mmol in 2 ml ethanol) was added. Then the reaction mass was stirred at 50 °C and the progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (2 × 10 ml). The organic layer was washed with water, saturated brine solution and dried over anhydrous sodium sulfate. The combined organic layer was evaporated under reduced pressure and thus obtained crude product was further purified by column chromatography with ethyl acetate: n-hexane (2: 8) as an eluent. The aqueous layer was then cooled to 0 °C; in which β-cyclodextrin reappeared as white solid. Thus obtained white solid mass then filtered and washed with water to recover β-cyclodextrin. It was noticed that, the cyclocondensation has been found to be completed within 2 to 3 hr, resulting in better to excellent yields of the benzothiazoles (Table 2.2, 3a-n).

Spectral data of representative compound of the series

Compound (3l): 2-(1,3-diphenyl-1H-pyrazol-4-yl)benzo[d]thiazole

$^1$H-NMR (300 MHz, CDCl$_3$) δ ppm = 7.31-7.61 (m, 8H, Ar-H), 7.74-7.84 (m, 5H, Ar-H), 8.02 (d, J = 9 Hz, 1H) and 8.66 (s, 1H, pyrazolyl H).

$^{13}$C-NMR (75 MHz, CDCl$_3$) δ ppm = 29.9, 76.8, 77.2 and 77.6 (Solvent impurities) 117.6, 119.6, 121.6, 122.8, 125.0, 126.4, 127.5, 128.4, 128.7, 129.3, 129.8, 129.9 and 153.3.

DART-MS (ESI$^+$ mode) (m/z, % intensity)= 354.15 (M+1, 100%), 355.16, 356.15, 353.15 and 357.16.
Table 2.2: Synthesis of 2-arylbenzothiazoles catalyzed by, β-CD\textsuperscript{a}(Scheme 2.8)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{b}</th>
<th>M. P. (°C)\textsuperscript{c}</th>
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<td>1</td>
<td></td>
<td>3a</td>
<td>92</td>
<td>112 – 113</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>3b</td>
<td>90</td>
<td>119 – 120</td>
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<td>3</td>
<td></td>
<td>3c</td>
<td>78</td>
<td>173 – 174</td>
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<td>4</td>
<td></td>
<td>3d</td>
<td>81</td>
<td>85 – 86</td>
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<td>5</td>
<td></td>
<td>3e</td>
<td>86</td>
<td>228 – 229</td>
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<td>3f</td>
<td>85</td>
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<td>83</td>
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<td>3j</td>
<td>76</td>
<td>102 -103</td>
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<td></td>
<td>3k</td>
<td>84</td>
<td>99 – 100</td>
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<td>12</td>
<td></td>
<td>3l</td>
<td>81</td>
<td>129 – 130</td>
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<td>13</td>
<td></td>
<td>3m</td>
<td>80</td>
<td>159 – 160</td>
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\[ \text{14} \quad \begin{array}{c}
\text{3n} \\
\text{77} \\
178 - 179
\end{array} \]

*Reaction conditions: 2-aminothiophenol (1 mmol), aryl aldehyde (1 mmol), β-cyclodextrin (1 mmol) in water (20 ml) at 50 °C.

bIsolated yields.

cThe known benzothiazoles synthesized by this method are having their melting points in good agreement with those reported in the literature.\textsuperscript{61,88}
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**$^1$H-NMR spectrum of 3l**

![H-NMR spectrum of 3l](image1)

**$^{13}$C-NMR spectrum of 3l**

![C-NMR spectrum of 3l](image2)
Mass spectrum of 3l
References


