Chemistry of Optically Active Cyanohydrins-Part 3:[1] Preparation and Reactions of (R)-2-Hydroxy-2-(naphthalen-1-yl)ethane- nitrile using (R)-Hydroxynitrile lyase from Prunus amygdalus. Antitumor and Antimicrobial Evaluation of the New Products

H.A.A. Yosef, Nihal O. Shaker*, Nesrin M. Morsy and M.R. H. Mahran*
Department of Organometallic and Organometalloid Chemistry, National Research Centre and Department of Chemistry, Faculty of Science (Girls), Al-Azhar University, Cairo, Egypt.

Cyanuration of 1- naphthaldehyde (1) yielded the racemic 2-hydroxy-2-(naphthalene-1-yl)ethanenitrile (R,S)-2. The same reaction can be completed by using acetone cyanohydrin (3) as a transcyanating agent. The optically active cyanohydrin enantiomer (R)-2 could be obtained by hydrocyanation of (1) in presence of (R)-hydroxynitrile lyase (R)-Pa HNL [EC4.1.2.10] from almonds (Prunus amygdalus) as a chiral catalyst. Cyanohydrin 2 in its racemic and optically active forms reacts with the isocyanate reagents 4a-e to give the carbamate derivatives (R,S)-5 and (R)-5, respectively. On the other hand, the reaction of (R,S)-2 and (R)-2 with the isothiocyanate and/or isothiocyanate reagents 6a-e gave the 4-imino-2-oxazolidinone derivatives, (R,S)-8 and (R)-8, respectively. Moreover, derivatization of (R)-2 with (S)-Naproxen® chloride (S)-10 gave the respective diastereomer (R,2S)-11. The postulated structures for the new products were supported with compatible elementary microanalyses and spectroscopic (IR, 1H NMR, MS) measurements. The antitumor and antimicrobial activities of some selected racemic new products and their respective optically active analogues were also endeavors. The structure-activity relationship (SAR) was also discussed.

Keywords: Aldehydes, Cyanohydrins, Enzymes, Enantioselective synthesis, Antitumor activity and Antimicrobial activity.

Cyanohydrins are ubiquitous in nature, expedient starting materials and valuable key building blocks for the one step synthesis of several classes of compounds such as α-hydroxy carboxylic acids[1-6]. Optically active cyanohydrins are also versatile intermediates in organic synthesis and have received considerable amount of

*Corresponding author.
E-mail address: mohamed_rh_mahran@yahoo.com
interest particularly during the last three decades\(^{(1,3,7,8)}\). A number of methods for the preparation of optically pure cyanohydrins have been developed using various chiral catalysts such as chiral complexes with titanium\(^{(9,10)}\), aluminum\(^{(11)}\) and boron\(^{(12)}\). The enantioselective synthesis of cyanohydrins has been also performed enzymatically by means of hydroxynitrile lyases (oxynitrilases) from different plant sources\(^{(4,13)}\). This approach is rather precise, clean and cheap. It entails a high degree of stereoselectivity leading to optically pure chiral cyanohydrins\(^{(2,14-17)}\).

**Results and Discussion**

**Chemistry**

Treatment of 1-naphthaldehyde (1) with aqueous potassium cyanide in presence of a saturated solution of sodium metabisulphite (Na\(_2\)S\(_2\)O\(_5\)) yielded 2-hydroxy-2-(naphthalene-1-yl) ethanenitrile (R,S)-2 in a 90% yield. Formation of (R,S)-2 from compound 1 in a yield value of 80% can be completed by using acetone cyanohydrin (3) as a transcyanating agent\(^{(18,19)}\) (Scheme 1).

\[
\text{HCN} \quad \text{KCN} / \text{Na}_2\text{S}_2\text{O}_5 \\
\text{(R)-oxynitrilase (from almonds)} \quad (\text{CH}_3)\text{C(OH)CN} \\
\text{1} \quad (\text{CH}_3)\text{C}=\text{O} \\
\text{Powdered almond meal} \quad \text{isopropyl ether} \\
\text{H} = 94 \%, [\alpha]_{D25} = +140 \\
\text{(R)-2} \quad (\text{R},S)\text{-2} \\
\text{IR spectrum of (R,S)-2 (KBr, v_{max}, cm}^{-1}) showed strong absorption bands at 3415 (O—H), 2240 (\text{C}=\text{N}) and 1625, 1598 (aromatic C=C). Its H NMR spectrum (DMSO-\text{d}_6, \delta \text{ ppm}) showed signals at 4.60 (brs, 1H, \text{OH}, \text{D}_2\text{O-exchangeable}), 6.00 (s, 1H, CHCN) and 7.10 – 8.20 (m, 7H, aromatics).
On the other hand, the optically active \((R)-2\)-hydroxy-2-(naphthalene-1-yl) ethanenitrite \((R)-2\) could be obtained by the hydrocyanation of 1 directly using \((R)\)-oxynitritase [EC4.1.2.10] from almonds which is a rich source of this enzyme\(^{20}\). Compound \((R)-2\) has been separated as yellow crystals in yield of 93% and a specific rotation value \([\alpha]_D^{25}\) of +140. Moreover, compound \((R)-2\) could be also obtained by using acetone cyanohydridin (3) as a transcyanating agent in the presence of powdered defatted almond meal (cf. Experimental). This meal provides an inexpensive catalyst; the use of which avoids the need to purify and immobilize the enzyme\(^{19}\).

Both of racemic and optically active forms of cyanohydridin 2 undergo a number of transformations which involve the hydroxyl function in their molecules.

Thus, treatment of \((R,S)-2\) with the isocyanates 4a-c in dry toluene and in the presence of triethylamine (TEA) at room temperature afforded the respective carbamate products \((R,S)-5a-c\) (Scheme 2).

\[\text{Scheme 2. Synthesis of cyanonaphthalen-1-yl)methyl carbamate derivatives (R,S)-5a-c.}\]

The structural reasonings for cyanonaphthalen-1-yl methyl isopropylcarbamate \((R,S)-5a\), taken as a representative example, are:

a) Compatible elementary and molecular weight determination (MS) corresponded to \(\text{C}_{16}\text{H}_{16}\text{N}_{2}\text{O}_{2}\) (268.31).

b) Its IR spectrum (KBr, \(v_{\text{max}}, \text{ cm}^{-1}\) ) showed strong absorption bands at 3352 (N—H), 3020 (aromatic C—H), 2974, 2928 (aliphatic C—H), 2195 (C≡N), 1727 (C=O, ester), 1602, 1513 (aromatic C=C) and at 1223 (C—O, stretching).

c) The HNMR spectrum of \((R,S)-5a\) (DMSO-\(d_6\), 6 ppm) revealed the presence of signals at 1.17 (d, \(\text{J}_{\text{HH}} = 7.0 \text{ Hz}\), 6H, (CH\(\text{3}_2\))CH), 3.88 (septet, \(\text{J}_{\text{HH}}=7.0 \text{ Hz}, 1\text{H}, \text{CH}(\text{CH}_3)_2\)), 4.74 (s, 1H, CH-O) and at 7.03 – 8.08 (m, 7H, aromatics).

\(\text{Egypt. J. Chem. 57, No. 5, 6 (2014)}\)
d) The mass spectrum of compound \( (R,S) \)-5a revealed the molecular ion peak at \( m/z \) 268 (13.66 \%).

On the other hand and under similar conditions, the oxazolidinone derivatives 8a-e have been obtained, as exclusive products, from the reaction of cyanohydrin \( (R,S) \)-2 with the isocyanates 6a-e. Apparently, compounds 8a-e have been formed through an intramolecular heterocyclization of the carbamate intermediates 7a-e (Scheme 3).

\( (R,S) \)-4-Imino-3-(2-methoxyphenyl) -5- (naphthalene-1-yl) oxazolidin-2-one (8b), as an example, was given the assigned structure due to the following reasons:

a) Compatible elementary and molecular weight determination of \( (R,S) \)-8b (MS: \( M^+ \) at \( m/z \) 332, 100 \%) corresponded to a molecular formula of C20H16N2O3 (332.35).

b) The IR spectrum revealed the absence of C=\( \equiv \)N group absorption around 2200 cm \(^{-1} \). However, it showed two strong absorption bands at 1779 and 1690 cm \(^{-1} \) which could be attributed to a lactonic carbonyl and an exocyclic C=\( \equiv \)N groups, respectively. The spectrum showed also bands at 3259 (N–H), 3069 (aromatic C–H), 1601, 1505 (aromatic C=C), 1165 (C–O, stretching).

c) The \( ^1H \) NMR spectrum of \( (R,S) \)-8b (DMSO-\( d_6 \), \( \delta \) ppm) revealed the presence of signals at 3.89 (s, 3H, OCH\(_3\)), 6.73 (s, 1H, CH-O) and 6.80 – 8.33 (m, 12H, aromatics and NH).

\[
\begin{array}{c}
\text{(R,S)-2} \\
\text{6a-e} \\
\text{To} \text{U} \text{lene, \text{TEA} } \text{r.t.} \\
\text{(R,S)-7a-e} \\
\text{6,7,8a. R= n-C}_4\text{H}_9, \text{X=O} \\
b. \text{R= 2-CH}_3\text{O-C}_6\text{H}_4, \text{X=O} \\
c. \text{R= 2,4-Cl}_2\text{-C}_6\text{H}_3, \text{X=O} \\
d. \text{R= 3,4-Cl}_2\text{-C}_6\text{H}_3, \text{X=O} \\
e. \text{R= C}_6\text{H}_5\text{-C(O)-, X=S} \\
\text{(R,S)-8a-e} \\
\end{array}
\]

Scheme 3. Synthesis of the racemic oxazolidinone derivatives \( (R,S) \)-8a-e.

d) The mass spectrum of compound \( (R,S) \)-8b (Scheme 4) showed the molecular ion peak \([M^+\]) at \( m/z \) 332 (100 \%, base peak). The radical cations a and b at \( m/z \) 304 (20.0 \%) and 288 (26.5 \%) can result via expulsion of CO and

\[\text{Egypt. J. Chem. 57, No. 5, 6 (2014)}\]
CO₂ molecules from the molecular ion peak, respectively. Such fragmentation pattern is frequent in the mass spectra of several lactones. Loss of a methoxy radical from b can afford cation c (m/z 257, 30.1 %) which undergoes a cleavage at axis x to give the naphthyl cation d (m/z 127, 35.57 %). The obtained, as exclusive products, from the reaction of cyanohydrin (R,S)-2 with the molecular ion peak can also lose a methoxyphenyl radical to give cation (m/z 255, 21.5%).

Scheme 4. The mass spectrum of compound (R,S)-8b.
In the same sense, the optically active enantiomers (R)-5a-c and (R)-8a-e could be also obtained upon reacting (R)-2 with reagents 4a-c and 6a-e (cf. Schemes 2 & 3), respectively.

Fig. 1. Structures of the optically active carbamate and oxazolidinone derivatives (R)-5a-c and (R)-8a-e, respectively.

Compatible elementary micranalyses as well as spectroscopic measurements were gained for all adducts. The specific rotations [α]D/25 and yields of the optically active forms (R)-5a-c and (R)-8a-e are represented in Table 1.

TABLE 1. The specific rotations and yields of the optically active carbamates (R)-5a-c and oxazolidinones (R)-8a-e.

<table>
<thead>
<tr>
<th>Compound</th>
<th>[α]D/25</th>
<th>Yield %</th>
<th>Compound</th>
<th>[α]D/25</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-5a</td>
<td>+ 97</td>
<td>83</td>
<td>(R)-8b</td>
<td>+ 20</td>
<td>90</td>
</tr>
<tr>
<td>(R)-5b</td>
<td>+ 143</td>
<td>82</td>
<td>(R)-8c</td>
<td>+ 100</td>
<td>89</td>
</tr>
<tr>
<td>(R)-5c</td>
<td>- 80.5</td>
<td>88</td>
<td>(R)-8d</td>
<td>+ 99.6</td>
<td>85</td>
</tr>
<tr>
<td>(R)-8a</td>
<td>+ 130</td>
<td>80</td>
<td>(R)-8e</td>
<td>+ 104</td>
<td>92</td>
</tr>
</tbody>
</table>

The use of (S)-Naproxen® (9) as a derivatizing agent to determine the optical purity of organic compounds\(^\text{22}\) and as a chiral resolving agent for converting...
racemates to a mixture of diastereomers\textsuperscript{(23, 24)} is very well recognized. In the present study, it has been found that derivatization of cyanohydrin (R)-2 with (S)-Naproxen chloride (S)-10 proceeds in the presence of pyridine to give the respective diastereomer, namely, (2S)-((R)-cyano (naphthalene-1-yl)methyl)-2-(6-methoxynaphthalen-2-yl)propanoate (R,2S)-11 (Scheme 5). The (S)-naproxen 9 used to prepare 11 was obtained by its extraction from commercially available tablets with chloroform\textsuperscript{(22)}. The acid chloride (S)-10 was prepared by reacting (S)-9 with oxalyl chloride in hexane\textsuperscript{(23)}.

\[ \text{(S)-9} \xrightarrow{(\text{COCl})_2 \text{hexane}} \text{(S)-10} \]

\[ \text{(R,2S)-11} \xrightarrow{\text{CH}_2\text{Cl}_2 / \text{pyridine}} \text{(R)-2} \]

\( \text{de} = 94 \% \), \([\text{d}]^{25} = +121.3 \)

\textbf{Scheme 5. Diastereomeric derivatization of (R)-2 with (S)-naproxene chloride (S)-10.}

The H NMR spectrum of compound 11 (CDCl\textsubscript{3}, \( \delta \) ppm) showed two doublets (each with \( J_{HH} = 6.8 \text{ Hz} \)) at 1.59 ppm and 1.63 ppm which are attributed to \( (\text{CH}_3\text{CH}) \)-protons of \( (R,2S)-11 \) (the major) and \( (S,2S)-11 \) (the minor) diastereomers, respectively. Comparable evaluation of the integral levels of these two signals indicated that \( (R,2S)-11 \), the major diastereomer, was obtained in a diastereomeric excess \( (\text{de}) \) value of 94%. This value reflects the enantiomeric excess of the starting cyanohydrin \( R)-2 \) (ee 94 %). The spectrum showed also signals at 3.91 (s, 3H, OCH\textsubscript{3}), 4.03 (q, \( J_{HH} = 6.8 \text{ Hz} \), 1H, CH\textsubscript{3}CH\textsubscript{3}), 6.90 – 8.10 (m, 13H, aromatics). The IR spectrum (KBr, \( v_{\text{max}} \), cm\textsuperscript{-1}) of \( (R,2S)-11 \) disclosed the presence of absorption bands at 3068 (aromatic C–H), 2960, 2850 (aliphatic C–H), 1750 (C=O, ester), 1606 (aromatic C=C) and 1183 (C–O, ester). The mass spectrum of \( (R,2S)-11 \) revealed the presence of the molecular ion peak [M\textsuperscript{+}] at m/z 395 (23%). The spectrum also showed ion peaks at m/z 185 (cation a), 166 (cation b) and 127 (cation c) which are expected from cleavage of [M\textsuperscript{+}] under electron bombardment.

The hydroxyl function in the cyanohydrin 2 can also be acylated by long chain acyl halides, e.g. stearoyl chloride. The reaction proceeds in dry methylene chloride to give brown crystals formulated as (R,S)-cyano(naphthalene-1-yl) methyl stearate (R,S)-12 (Scheme 6).


Its IR spectrum (KBr, cm⁻¹) disclosed the presence of strong absorption bands at 3050 (aromatic C—H), 2916, 2849 (aliphatic C—H), 1764 (C=O, ester) and 1146 (C—O, stretching). The C≡N group appeared as a weak band at 2200 cm⁻¹. The HNMR spectrum of 12 (DMSO, δ ppm) revealed the presence of signals at 0.84 (t, J_HH=6.4, 3H, -C-CH₃), 1.25–1.59 (m, 30H, (CH₂)₁₅), 2.27 (t, J_HH=7.5 Hz, 2H, CH₂-C(O)), 7.06 – 8.09 (m, 7H, aromatics) and 7.21 (s, 1H, CH-CN). Correct elementary analyses and molecular weight determination (MS) corresponded to C₃₉H₄₃NO₂ (m/z 449, M⁺, 80%). The molecular ion peak undergoes cleavage at axis x to afford cation a at m/z 182 and cation b at m/z 267 (Scheme 7). Loss of a HCN molecule from cation a gives cation c at m/z 155 which can eject CO molecule to afford cation d at m/z 127. The molecular ion peak can also undergo cleavage at axis y to afford cations e and f at m/z 165 and m/z 284, respectively.
Scheme 7. The mass spectrum of compound (R,S)-12.

Biological evaluation

Antitumor activity

Chemotherapy is a major approach for both localized and metastasized cancer\(^{25}\). Therefore, five of the newly synthesized compounds were screened for their \textit{in vitro} cytotoxic and growth inhibitory activities against human breast (MCF 7), colon (HCT 116) and liver (HEPG 2) carcinoma, in comparison with the activity of the known anticancer Doxorubicin (DOX) as a reference drug. The sulphorhodamine B (SRB) method\(^{26}\) was used for the assay of the cytotoxic activity which is expressed as IC\(_{50}\) \(\mu\)g/ml (the dose that reduces survival to 50%). The screening results are compiled in Table 2. The relation between the surviving fraction and drug concentrations are graphically plotted to get the survival curves of the three tumor cell lines (Fig. 3-5). It is evident that the racemic oxazolidinone derivative (R,S)-8d is the most of the tested compounds that shows the highest cytotoxic and growth inhibitory activities against the three
tested human carcinoma cell lines and even higher than the activity of the anticancer reference drug (Doxorubicin, DOX) (Tables 2 & 3 and Fig. 3-5). Its optically active isomer (R)-8d, on the other hand, showed similar potency only against liver carcinoma HEPG 2 (Tables 1 & 2 and Fig. 3). Apparently, the antitumor activities of the tested compounds seem to be correlated with the N-substituent on the oxazolidinone nucleus. Against liver carcinoma HEPG 2, as an example, the potency decreases in the order (R,S)-8d > (R)-8d > (R,S)-8e < (R,S)-8b (Table 3).

**TABLE 2. The cytotoxic activities of the tested compounds against MCF 7, HCT 116 and HEPG 2 tumor cell lines.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC₅₀(μg/ml)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCF-7</td>
<td>HCT 116</td>
<td>HEPG 2</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>2.97</td>
<td>3.74</td>
<td>5.50</td>
</tr>
<tr>
<td>(R,S)-8b</td>
<td>2.82</td>
<td>3.74</td>
<td>4.00</td>
</tr>
<tr>
<td>(R,S)-8d</td>
<td>2.51</td>
<td>3.13</td>
<td>2.82</td>
</tr>
<tr>
<td>(R,S)-8e</td>
<td>2.82</td>
<td>3.85</td>
<td>3.73</td>
</tr>
<tr>
<td>(R)-8d</td>
<td>3.43</td>
<td>4.19</td>
<td>3.12</td>
</tr>
</tbody>
</table>

**TABLE 3. The cytotoxic activities of the tested compounds against MCF 7, HCT 116 and HEPG 2 tumor cell lines according to their descending orders of activities.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC₅₀(μg/ml)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCF-7</td>
<td>HCT 116</td>
<td>HEPG 2</td>
</tr>
<tr>
<td>(R,S)-8d</td>
<td>2.51</td>
<td>(R,S)-8d</td>
<td>3.13</td>
</tr>
<tr>
<td>(R,S)-8b</td>
<td>2.82</td>
<td>(R,S)-8b</td>
<td>3.74</td>
</tr>
<tr>
<td>(R,S)-8e</td>
<td>2.82</td>
<td>Doxorubicin</td>
<td>3.74</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>2.97</td>
<td>(R,S)-8e</td>
<td>3.85</td>
</tr>
<tr>
<td>(R)-8d</td>
<td>3.43</td>
<td>(R)-8d</td>
<td>4.19</td>
</tr>
</tbody>
</table>

Fig. 3. The surviving fraction as a function of drug concentrations of the investigated compounds compared with Doxorubicin (reference drug) against MCF-7 tumor cell line.

Fig. 4. The surviving fraction as a function of drug concentrations of the investigated compounds compared with Doxorubicin (reference drug) against HCT 116 tumor cell line.
Antimicrobial activities

Some of the newly prepared racemic compounds and/or their respective optically active forms of carbamates 5 and oxazolidinones 8 were screened in vitro against some bacteria (as *Escherichia coli*, *Staphylococcus aureus* and some fungi (as *Aspergillus flavus* and *Candida albicans*) using a modified Kirby-Baure disc diffusion method\(^\text{27}\). Tetracycline and Amphotericin B were taken as reference drugs for antibacterial and antifungal screenings, respectively. The results are compiled in Table 4 and graphically illustrated in Fig. 6. None of the examined compounds except \((R,S)-8d\) showed any antifungal activity on the tested microorganism. Except for compounds, \((R,S)-8b,e\) the other tested compounds exhibited moderate to high activity against G and G bacteria. While the racemic compound \((R,S)-8e\) showed no antibacterial activity, its optically active form \((R)-8e\), on the other hand, recorded high activity against the tested bacteria. This might be of a particular significance in the light of the well established correlation between the biological activity and stereochemical aspects\(^\text{28}\). These results also supplement to the well established correlation between the presence of the carbamate group and / or the oxazolidinone ring and the antimicrobial activity\(^\text{29-32}\).

\[\text{Fig. 5. The surviving fraction as a function of drug concentrations of the investigated compounds compared with Doxorubicin (reference drug) against HepG2 tumor cell line.}\]
TABLE 4. Antimicrobial activity of some racemic and optically active cyanohydrin
derivatives expressed as inhibition zone diameter (mm/mg sample).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibition zone diameter (mm/mg sample).</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibacterial agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>26</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungal agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--</td>
<td>--</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>(R,S)-5a</td>
<td>13</td>
<td>14</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R,S)-5c</td>
<td>13</td>
<td>13</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R,S)-8a</td>
<td>15</td>
<td>15</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R,S)-8b</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R,S)-8c</td>
<td>15</td>
<td>14</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R,S)-8d</td>
<td>14</td>
<td>14</td>
<td>0.0</td>
<td>13</td>
</tr>
<tr>
<td>(R,S)-8e</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R)-5a</td>
<td>12</td>
<td>13</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R)-5b</td>
<td>12</td>
<td>12</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R)-5c</td>
<td>15</td>
<td>13</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R)-8a</td>
<td>13</td>
<td>12</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R)-8c</td>
<td>13</td>
<td>13</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R)-8d</td>
<td>15</td>
<td>13</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>(R)-8e</td>
<td>15</td>
<td>15</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

< 7 mm (non active), 7-9 mm (slightly active), 10-12 mm (moderately active), ≥ 13 mm (highly active).
Fig. 6. The antibacterial and antifungal activities of the investigated compounds against *E. coli*, *S. aureus* (bacteria) and *A. flavus*, *C. albicans* (fungi) compared to tetracycline and amphotericin B, respectively.

**Conclusion**

The present study reports on simple and efficient approaches for the preparation of new racemic and optically active carbamates and oxazolidinone derivatives, (R,S)-5a-c, (R)-5a-c and (R,S)-8a-e, (R)-8a-e, respectively. Cyanohydrins (R,S)-2 and (R)-2 were successfully used as suitable starting materials for implementing these goals. Some of the new compounds revealed pronounced *in vitro* antitumor activities when tested against human breast (MCF 7), colon (HCT 116) and liver (HEPG 2) carcinoma cell lines. The most promising results against these cell lines were recorded by compound (R,S)-8d. It showed IC50 values which are much less in values than those recorded by the reference drug Doxorubicin (DOX). Moreover, most of the new compounds inhibited the growth of all tested bacterial organisms which are rather close to the potency of the reference drug (Tetracycline). This is probably due to the presence of the carbamate group and/or the oxazolidinone ring which have antimicrobial activity29-32.

**Experimental**

The reactions of air-sensitive reagents were carried out in flame-dried glassware under an atmosphere of dry argon. Solvents were rigorously dried according to literature procedures. Aldehyde 1 is commercially available (Aldrich Co.) and was purified directly before use. The racemic cyanohydrin
(R,S)-2 was prepared according to a known procedure(33). Chromatography was performed using silica gel, grain size 0.040-0.063 (Merck). The (R)-hydroxynitrilase (HNL) was extracted(34) and assayed(35) according to established references. Naproxen is commercially available and naproxen chloride is prepared according to a procedure developed by Solis et al. (22). Melting points were recorded on an electrothermal melting point apparatus and were uncorrected. pH measurements were made on Precisa Digital pH-Meter pH 900 with Ag/AgCl electrode. The optical rotations were recorded on Perkin Elmer polarimeter 241 LC and /or Carl Zeiss 212503 polarimeter. The specific rotation values [α] D/25 = α/c.d are expressed in (°,L) / (Kg. dm) where path length (d) = 10 cm, concentration (c) = 10 mg ml and α is the measured angle of rotation in degrees (°). A Shimadzu UV-2401 PC UV-VIS Recording Spectrophotometer was used in assay of the enzyme. The infrared spectra were recorded either neat or from KBr disks using Bruker Vector 22 Spectrophotometer and/or JASCO FT/IR-300E Fourier Transform Infrared Spectrophotometer. H NMR spectra were recorded on Varian Gemini MHz 200 at 200 MHz and/or JEOL JNM-EX 270 at 270 MHz. The mass spectra were recorded on Finnigan SSQ 7000 Spectrometer at 70eV. Correct microanalysis for C, H, Cl, N and S were gained for the new products and were carried out at the Microanalytical Unit, Cairo University, Cairo, Egypt. The antitumor activity was carried out at the Cancer Biology Department, National Cancer Institute, Cairo University, Egypt. The antimicrobial evaluation results were obtained from the Microanalytical Unit, Cairo University, Egypt.

_Synthesis of the racemic cyanohydrin (R,S)-2(33)_

In a three necked flask equipped with a mechanical stirrer and a dropping funnel, a saturated solution of sodium metabisulphite (50 g in 70 ml water) was added dropwise to a mixture of aldehyde 1 (0.1 mol, 13.6 g) and potassium cyanide solution (0.1 mole, 6.6 g in 20 ml of freshly distilled water). During the initial stages of addition, the reaction mixture was cooled by adding crushed ice in several portions through the third neck. After completion of addition (30 min.), the reaction mixture was stirred for further 6 hr at room temperature then extracted with diethyl ether (3 x 100 ml). The combined organic extracts were washed with water (2 x 50 ml) and dried over anhydrous sodium sulfate and filtered. The ethereal filtrate was evaporated under reduced pressure to leave a residue which was dried well _in vacuo_ to afford compound (R,S)-2.

(R,S)-2-hydroxy-2-(naphthalene-1-yl)ethanenitrile (R,S)-2

Yellow crystals, m. p. 110 –112 °C, yield 85%. IR (KBr, v max. cm⁻¹): 3415 (br, O—H), 2240 (C≡N), 1625, 1598 (C≡C, aromatic).  H NMR (DMSO, δ ppm): 4.60 (bs, 1H, OH, D2O exchangeable), 6.00 (s, 1H, CHCN), 7.10 – 8.20 (m, 7H, ArH). Anal. Calcd (%) for C12H9NO (183.21): C, 78.67; H, 4.95; N, 7.65. Found (%): C, 78.57; H, 4.98; N, 7.60.
Synthesis of compound (R,S)-2 using acetone cyanohydrin (3) as a transcyanating agent

To a stirred solution of aldehyde 1 (0.01 mole, 1.56 g) in diisopropyl ether (20 ml), was added acetone cyanohydrin\(^{14}\) (0.015 mol, 1.2 ml) followed by sodium hydroxide (15 ml of 1M solution) at room temperature. After stirring for further 6 hr, the reaction mixture was followed up as described in the above procedure to give \((R,S)-2\)-hydroxy-2-(naphthalene-1-yl)ethanenitrile \((R,S)-2\) as yellow crystals with m. p. 108-111 °C and in a yield value of 78%. For further characterizations, see above.

**Preparation of the optically active cyanohydrin (R)-2**

**Extraction of \((R)-\)Oxynitrilase enzyme (HNL)\(^{14}\)**

1) The almond powder (600 g) was stirred mechanically in 2.5 litre of dry freshly distilled diisopropyl ether (IPE) for 24 hr at room temperature.

2) The defatted almond meal, so obtained was swollen in 500 ml of citrate buffer solution (2.1 g of citric acid monohydrate in 50 ml of distilled water, while adjusting the pH value to 3.3 with stirring for 16 hr at 4 °C.

3) The meal was filtered off and the enzyme filtrate was diluted 40 times with phosphate buffer pH 6.5. The enzyme was assayed and evaluated according to a given method\(^{15}\).

**Preparation of the optically active cyanohydrin (R)-2**

1. To a solution of potassium cyanide (0.2 mol, 13 g) in distilled water (30ml) and isopropyl ether (50 ml), was added orthophosphoric acid (0.2 mol, 13.7 ml) dropwise with stirring within 5 min at 0 °C. After completion of addition, the reaction mixture was stirred for further 10 min at room temperature. After removal of the cooling bath, the ethereal layer containing HCN gas was separated and used directly in the next step.

2. To a mixture of aldehyde 1 (0.1 mol, 15.6 g) and the crude enzyme extract in diisopropyl ether (30 ml) was added the ethereal HCN solution (prepared in the first step) dropwise with stirring at 0 °C. After completion of addition (30 min), the reaction mixture was stirred for further 16 hr. The cooling bath was removed and the reaction mixture was stirred vigorously with an excess of saturated sodium chloride solution (200 ml) and diisopropyl ether (100 ml) for 30 min. The ethereal layer was separated, washed with distilled water (2 x 50 ml) and dried over anhydrous sodium sulphate. After filtration the ether solution was evaporated under reduced pressure to leave a residue which was dried well \emph{in vacuo} to afford the optically active cyanohydrin \((R)-2\).

\((R)-2\)-hydroxy-2-(naphthalene-1-yl)ethanenitrile \((R)-2\): [\(\alpha\)]\(D\)\(25 = +140\), enantionic excess (ee) = 94%. Yellow crystals, m.p. 111–112 °C, yield 93 %. For further characterizations, see above.

\emph{Egypt. J. Chem.} 57, No. 5, 6 (2014)
Preparation of (R)-2 using acetone cyanohydrin as a transcyanating agent
To a mixture of 1-naphthaldehyde (1) (0.01 mole, 1.56 g) and the crude enzyme extract in diisopropyl ether (5 ml) was added acetone cyanohydrin (3) (0.015 mole, 102 ml) at room temperature. After stirring for further 6 hr, the reaction mixture was worked up as described in the above procedure to give (R)-2-2-hydroxy-2-(naphthalen-1-yl)ethanenitrile (R)-2in yield of 84 %.

Synthesis of the carbamate derivatives (R,S)-5a-c and their respective optically active forms (R)-5a-c
General procedure
To a stirred mixture of the appropriate racemic and/or optically active cyanohydrin (R,S)-2 or (R)-2 (0.01 mole, 1.83 g) and triethylamine (10 μl) in dry toluene (10 ml) was added a solution of the appropriate isocyanate 4a-c (0.012 mole) in toluene (5 ml) at 0°C under dry argon atmosphere. After stirring the reaction mixture for further 48 hr at room temperature, the volatile materials were removed under reduced pressure where the residual substance was collected, washed with light petroleum, dried and recrystallized from a suitable solvent to give the corresponding carbamate derivatives (R,S)-5a-c and / or (R)-5a-c, respectively. The specific rotations and yields of the optically active forms (R)-5a-c are compiled in Table 1. (c.f. Discussion). For further characterizations, see below.

(R,S)-Cyano(naphthalen-1-yl)methyl iso-propylcarbamate (R,S)-5a
Colorless crystals (petroleum ether 80-100 °C), m.p. 82 – 84 °C, yield 89 %. IR (KBr, νmax, cm⁻¹): 3352 (N-H), 3020 (C=H, aromatic), 2974 (C=H aliphatic, asymmetric), 2928 (C=H aliphatic, symmetric), 2195 (C≡N), 1727 (C=O), 1602, 1513 (C=C, aromatic), 1223 (C=O, ester). H NMR (CDCl₃, δ ppm): 1.17 (d, J=7.0 Hz, 6H, CH(CH₃)₂), 3.88 (septet, J=7.0 Hz, 1H, -CH(CH₃)₂), 4.74 (s, 1H, HC-CN), 7.03 – 8.08 (m, 8H, ArH and NH). MS (El, 70 eV): m/z (%) 268 (13.66) [M⁺]. Anal. Calcd (%) for C₁₆H₁₆N₂O₂ (268.31): C, 71.62; H, 6.01; N, 10.44. Found (%): C, 71.69; H, 5.97; N, 10.39.

(R,S)-Cyano(naphthalen-1-yl)methyl cyclohexylcarbamate (R,S)-5b
Pale yellow crystals (toluene), m.p. 93 – 95 °C, yield 80 %. IR (KBr, νmax, cm⁻¹): 3306 (N-H), 3062 (C=H, aromatic), 2929 (C=H aliphatic, symmetric), 2854 (C=H aliphatic, symmetric), 2184 (C≡N), 1702 (C=O), 1602, 1539 (C=C, aromatic), 1132 (C=O, ester). H NMR (CDCl₃, δ ppm): 1.08 - 2.01 (m, 11H, CH₂, cyclohexyl), 3.45 (1H, NH, D₂O exchangeable), 4.82 (s, 1H, HC-CN), 7.25 – 8.05 (m, 7H, ArH). Anal. Calcd (%) for C₁₉H₂₀N₂O₂ (308.37): C, 74.00; H, 6.54; N, 9.08. Found (%): C, 73.93; H, 6.60; N, 8.99.

Egypt. J. Chem. 57, No. 5, 6 (2014)
(R,S)-Cyano(naphthalen-1-yl)methyl benzylcarbamate (R,S)-5c

Colorless crystals (toluene), m.p.183 –185 °C, yield 88%. IR (KBr, vmax cm⁻¹): 3398 (N—H), 3095 (C—H, aromatic), 2928 (C—H, aliphatic), 2200 (C≡N), 1729 (C=O), 1519 (C=C, aromatic), 1114 (C—O, ester).¹ ¹H NMR (CDCl₃, δ ppm): 4.39 (s, 2H, CH₂, benzyl), 5.20 (s, 1H, HC-CN), 7.28 – 8.30 (m, 13H, ArH and NH). Anal. Calcd (%) for C₂₀H₁₆N₂O₂ (316.35): C, 75.93; H, 5.10; N, 8.66. Found (%): 75.86; H, 5.12; N, 8.78.

Synthesis of the oxazolidinone derivatives (R,S)-8a-e and their respective optically active forms (R)-8a-c

General procedure

The racemic and/or optically active cyanohydrin (R,S)-2 or (R)-2 were reacted with the appropriate isocyanate 6a-c, according to the above procedure, to give the corresponding oxazolidinone derivatives (R,S)-8a-e and/or (R)-8a-e, respectively. The specific rotations and yields of the optically active forms (R)-8a-c are compiled in Table 1 (c.f. Discussion). For further characterizations, see below.

(R,S)-3-Butyl-4-imino-5-(naphthalen-1-yl)oxazolidin-2-one (R,S)-8a

Pale yellow crystals (toluene), m.p.105 – 107 °C, yield 85 %. IR (KBr, cm⁻¹), 3323 (N—H), 2933, 2856 (C—H, aliphatic), 1782 (C=O, lactone), 1677 (C=N, exocyclic), 1601 (C=C, aromatic), 1264 (C—O stretching, lactone).² ¹H NMR (DMSO, δ ppm): 0.92 (t, J₆H₆= 7.8 Hz, 3H, CH₃), 1.50 – 1.32 (m, 4H, (CH₂)₂), 3.25 (t, J₅H₅= 8.0 Hz, 2H, H₂C-N), 7.61 – 8.09 (7H, ArH, m). MS (EI, 70 eV): m/z (%) 282 (40.78) [M⁺]. Anal. calcd (%) for C₁₇H₁₈N₂O₂ (282.34): C, 72.32; H, 6.43; N, 9.92. Found (%): C, 72.29; H, 6.47; N, 9.87.

(R,S)-4-Imino-3-(2-methoxyphenyl)-5-(naphthalen-1-yl)oxazolidin-2-one (R,S)-8b

Colorless crystals (toluene), m.p.172 – 174 °C, yield 82 %. IR (KBr, vmax cm⁻¹): 3259 (N—H), 3069 (C—H, aromatic), 1779 (C=O, lactone), 1690 (C=N, exocyclic), 1601, 1505 (C=C, aromatic) 1165 (C—O stretching, lactone).³ ¹H NMR (CDCl₃, δ ppm): 3.89 (s, 3H, OCH₃), 6.73 (s, 1H, HC-CN), 6.8 – 8.33 (m, 12H, ArH and NH). MS (EI, 70 eV): m/z (%) 332 (100) [M⁺], 304 (20) [M⁺ – CO], 288 (26.5) [M⁺ – CO₂]. Anal. Calcd (%) for C₂₀H₁₆N₂O₃ (332.35): C, 72.28; H, 4.85; N, 8.43. Found (%): C, 72.16; H, 4.89; N, 8.47.

(R,S)-3-(2,4-Dichlorophenyl)-4-imino-5-(naphthalen-1-yl)oxazolidin-2-one (R,S)-8c

Colorless crystals (THF), m.p.142 – 144, yield 85 %. IR (KBr, vmax cm⁻¹): 3303 (N—H), 3066 (C—H, aromatic), 1777 (C=O, lactone), 1672 (C=N, 1444, 1389 (C—O HCN), 1272 (C=N, exocyclic), 1157 (C—O stretching, lactone). MS (EI, 70 eV): m/z (%) 358 (100) [M⁺]. Anal. Calcd (%) for C₂₀H₁₆N₂O₂Cl₂ (358.39): C, 59.33; H, 4.49; N, 9.67. Found (%): C, 59.12; H, 4.53; N, 9.71.

Egypt. J. Chem. 57, No. 5, 6 (2014)
exocyclic), 1596 (C=C, aromatic), 1127 (C—O stretching, lactone), 810 (Cl—C, aromatic). H NMR (DMSO-<sup>d6</sup>, δ ppm): 6.33 (s, 1H, HC-CN), 7.60 – 8.20 (m, 10H, ArH), 8.77 (NH, D<sub>2</sub>O exchangeable). MS (EI, 70 eV): m/z (%) 370 (100) [M<sup>+</sup>], 374 (7) [M<sup>+</sup> + 4], 342 (3.1) [M<sup>+</sup> – CO], 326 (32.5) [M<sup>+</sup> – CO<sub>2</sub>]. Anal. Calcd (%) for C<sub>19</sub>H<sub>12</sub>C<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 61.47; H, 3.26; Cl, 19.10; N, 7.55. Found (%): C, 61.56; H, 3.21; Cl, 18.97; N, 7.51.

(R,S)-3-(3,4-Dichlorophenyl)-4-imino-5-(naphthalen-1-yl)oxazolidin-2-one (R,S)-8d

Colorless crystals (dioxane), m.p.208 – 210 °C, yield 87 %. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3367(N—H), 3117 (C—H, aromatic), 1770 (C=O, lactone), 1669 (C=N), 1610, 1581 (C=C, aromatic), 1128 (C—O stretching, lactone), 809 (Cl—C, aromatic). H NMR (CDCl<sub>3</sub>, δ ppm): 6.7 (s, 1H, HC-CN), 7.50 – 8.20 (m, 10H, ArH) and 8.10 (NH, D<sub>2</sub>O exchangeable). MS (EI, 70 eV): m/z (%) 370 (34.01) [M<sup>+</sup>], 374 (3) [M<sup>+</sup> + 4], 326 (22) [M<sup>+</sup> – CO<sub>2</sub>]. Anal. Calcd (%) for C<sub>19</sub>H<sub>12</sub>C<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 61.47; H, 3.26; Cl, 19.10; N, 7.55. Found (%): C, 61.57; H, 3.19; Cl, 18.94; N, 7.61.

(R,S)-3-(Benzyl)-4-imino-5-(naphthalen-1-yl)oxazolidin-2-thione (R,S)-8e

Yellow crystals (toluene), m.p.198 – 200 °C, yield: 79 %. IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3242 (N—H), 3100 (C—H, aromatic), 1700 (C=O, aryl), 1669 (C=N, exocyclic), 1610, 1576, (C=C, aromatic), 1199 (C=S, exocyclic). H NMR (CDCl<sub>3</sub>, δ ppm): 7.16 (s, 1H, HC-CN), 7.40 – 8.30 (m, 12H, ArH) and 12.73 (NH, D<sub>2</sub>O exchangeable). Anal. Calcd (%) for C<sub>20</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S: (346.40), C, 69.35; H, 4.07; N, 8.09; S, 9.26. Found (%): C, 69.38; H, 4.06; N, 8.01; S, 9.30.

**Determination of the enantiomeric excess of cyanohydrin (R)-2 by its derivatization with naproxen chloride (S)-10<sup>22</sup>**

**Step 1: Preparation of Naproxen Chloride (S)-10<sup>22</sup>**

Naproxen<sup>®</sup> (S)-9 (obtained from commercially available tablets after extraction with chloroform) (0.03 mole, 7g) was refluxed with freshly distilled oxalyl chloride (0.03 mole, 3.8 g, 2.6 ml) in dry hexane for 2 hr under dry argon atmosphere. The volatile materials were removed in vacuo to leave naproxen chloride (S)-10 as a pale yellow residue.

**Step 2: Addition of Naproxen Chloride to Cyanohydrin (R)-2**

A solution of naproxen chloride (S)-10 (from step 1), in 10 ml of dry methylene chloride, was added dropwise to a mixture of the optically active cyanohydrin (R)-2 with stirring at 0°C under dry argon atmosphere. The cooling bath was removed and the reaction mixture was stirred for further 3 hr at room

*Egypt J. Chem. 57, No. 5, 6 (2014)*
temperature. An additional volume of methylene chloride (30 ml) was added, then the reaction mixture was washed with a saturated solution of sodium carbonate (3 x 20 ml), distilled water (3 x 20 ml) and dried over anhydrous sodium sulphate. The solid materials were filtered off and the volatile materials were removed under reduced pressure. The solid product, so obtained, was collected from light petroleum and chromatographed on silica gel then eluted with petroleum ether 60-80 °C/acetone (8 : 2) to give (2S)-(R)-cyano(naphthalen-1-yl)methyl)-2-(6-methoxynaphthalen-2-yl)propanoate (R,2S)-11 in a diastereomeric excess (de) value of 94 % (H NMR) (cf. Discussion).

\[
\text{[a]D}_{25} = 121.3, \text{ de } 94 \% \text{ (H NMR)}. \text{ Colourless crystals, m.p. } 166 - 168 ^\circ \text{C, yield } 84 \%. \text{ (KBr, } v_{\text{max}}, \text{ cm}^{-1}) 3068 \text{ (C—H, aromatic), 2960 (C—H aliphatic, asymmetric), 2850 (C—H aliphatic, symmetric), 1750 (C=O, ester), 1606 (C=C, aromatic), 1183 (C—O stretching, ester). H NMR (CDCl}_3, \delta \text{ ppm): 1.59 (d, } J_{\text{HH}} = 6.8 \text{ Hz, 3H, CH}_3\text{-CH), 3.91 (s, 3H, OCH}_3\text{), 4.03 (q, } J_{\text{HH}} = 6.8 \text{ Hz, 1H, CH}_3\text{-CH), 6.90 - 8.10 (m, 13 H, ArH). MS (El, 70 eV): m/z (%). 395 (23) [M]^+}. \text{ Anal. Calc. (%) for C}_{26}\text{H}_{21}\text{NO}_3 (395.45): C, 78.97; H, 5.35; N, 5.34. Found (%) : C, 78.90; H, 5.38; N, 3.49.}

**Reaction of cyanhydrin (R,S)-2 with stearoyl chloride**

A solution of stearoyl chloride (0.01 mole, 2.67 g) in 10 ml of dry methylene chloride was added dropwise by a syring to a mixture of cyanohydrin (R,S)-2 (0.01 mole, 1.83 g) and pyridine (0.01 mole, 0.85 ml) in 10 ml dry methylene chloride with stirring at 0 °C under dry argon atmosphere. The cooling bath was removed and the reaction mixture was stirred for further 5 hr at room temperature. An additional volume of methylene chloride (30 ml) was added, then the reaction mixture was washed with a saturated solution of sodium carbonate (3 x 20 ml), distilled water (3 x 20 ml) and dried over anhydrous sodium sulphate. The solid materials were filtered off and the filtrate was evaporated under reduced pressure where the residual substance was collected and recrystallized from petroleum ether 80 – 100 °C to give the corresponding stearate ester (R,S)-12.

**Cyano(naphthalen-1-yl)methyl stearate (R,S)-12**

Brown crystals (Petroleum ether 40 – 60 °C, m.p. 46 – 47 °C, yield 78 %. (KBr, \( v_{\text{max}}, \text{ cm}^{-1} \): 3050 (C—H, aromatic), 2916 (C—H aliphatic, asymmetric), 2849 (C—H aliphatic, symmetric), 2200 (C=O, ester), 1146 (C—O stretching, ester). H NMR (DMSO-\( d_6 \), \( \delta \text{ ppm} \)): 0.84 (t, \( J_{\text{HH}} = 6.4, 3 \text{H, CH}_3\text{CH}_2 \)), 1.25 – 1.59 (m, 30H, (CH\( _2 \))_15), 2.27 (t, \( J_{\text{HH}}=7.5 \text{ Hz, 2H, CH}_2\text{-C(O)} \)), 7.21 (s, 1H, NC-CH\( _3 \)), 7.06 – 8.09 ( m. 7H, ArH). MS (El, 70 eV): m/z


Acknowledgement: Prof. M. R. H. Mahran extends much thankfulness and indebtedness to the Alexander von Humbold-Stiftung, Federal Republic of Germany, for the generous donation of the HPLC equipment.

References


Egypt. J. Chem. 57, No. 5, 6 (2014)


(Received 5/11/2014; accepted 3/12/2014)
K. A. Yosef et al.

Egypt. J. Chem. 57, No. 5, 6 (2014)

Khimya cianohidrinat neshchegia: chast' trit gospodardushchikh priparatov.

Tverdovat'sya (R,S)-2-2-hekrokse-2-(1-nafthalenil) cianochiprnyit neshchegia na sokrovanivii cianobidronit v chistom reshte.

Termoaktivnyi termobiding sostava 1-2-nafthalandeliksa izobutliulnit.

Keverostva izobutliulnit sostava 1-2-nafthalandeliksa izobutliulnit.

Keverostva izobutliulnit sostava 1-2-nafthalandeliksa izobutliulnit.

R.S.

2-1-nafthalandeliksa izobutliulnit.

(R,S)

4a-c

8a-c

10

11

12622

21611

1-2-nafthalandeliksa izobutliulnit.

(R,S)

(R,S)

(R,S)

(R,S)

(R,S)

(R,S)