Advanced Dihydropyridines as Novel Multidrug Resistance Modifiers and Reversing Agents

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1 Cancer and the Current Status in World .................. 202

2 Role of ABC Transporters .............................. 202
2.1 Structure of ABC Proteins ............................ 203
2.2 Role of Resistance in Cancer-The Players .............. 203
2.3 Basic Mechanism of MDR in Cancer ................... 204
2.4 Nomenclature, Basic Structure, and Membrane Topology of MDR Proteins 204

3 Substrate Specificity of MDR-ABC Transporter .......... 207

4 Cellular and Tissue Distribution of MDR-ABC Transporter 209

5 Molecular Mechanism of the Multidrug Pumps ........... 210

6 MDR Modulators ........................................ 212

7 DHPs as Potential MDR Reversal Agents ................. 217
7.1 Historical Background ............................... 217

8 Conclusions ............................................ 243

References .............................................. 244

Abstract Dihydropyridines (DHPs) are recognized as one of the Ca\(^{2+}\) channel-blockers as a number of clinically used drugs are derivatives of various DHPs. Despite this, these DHPs are significantly potent in cancer chemotherapy along with clinically used drugs. This family of compounds is potent inhibitors of P-glycoprotein (Pgp), which are the main cause of the efflux of toxins the cells. This review mainly focuses on the Pgp inhibitory property of DHPs. The literature collection includes the latest developments in this area. This comprehensive review could also encompass their synthetic methodology for the preparation of the most active Pgp inhibitor DHPs. This article specifically covers the MDR reversal activity. However, this article does not cover their cardiovascular or rest of the pharmacological activities shown of DHPs.
Keywords  Dihydropyridines (DHPs) · Multidrug resistance (MDR) ·
P-glycoprotein (Pgp)

1 Cancer and the Current Status in World

With more than 10 million new cases every year, cancer is one of the most
devastating diseases worldwide. The disease burden is immense, not only for
affected individuals but also for their relatives and friends. At the community
level, cancer has posed considerable challenges for the health care systems in
both poor and rich countries. The World Cancer Report (WCR) of 2007 pro-
vides a unique global view of cancer. It documents the frequency of cancer
in different countries and trends in cancer incidence and mortality as well as
describing the known causes of human cancer [1] (Table 1).

Table 1  The estimated numbers of new cases and deaths for each common cancer
type [2, 3]

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Estimated new cases</th>
<th>Estimated deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>67 160</td>
<td>13 750</td>
</tr>
<tr>
<td>Breast (Female – Male)</td>
<td>178 480–2030</td>
<td>40 460–450</td>
</tr>
<tr>
<td>Colon and Rectal (Combined)</td>
<td>153 760</td>
<td>52 180</td>
</tr>
<tr>
<td>Endometrial</td>
<td>39 080</td>
<td>7400</td>
</tr>
<tr>
<td>Kidney (Renal Cell) Cancer</td>
<td>43 512</td>
<td>10 957</td>
</tr>
<tr>
<td>Leukemia (All)</td>
<td>44 240</td>
<td>21 790</td>
</tr>
<tr>
<td>Lung (Including Bronchus)</td>
<td>213 380</td>
<td>160 390</td>
</tr>
<tr>
<td>Melanoma</td>
<td>59 940</td>
<td>8110</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma</td>
<td>63 190</td>
<td>18 660</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>37 170</td>
<td>33 370</td>
</tr>
<tr>
<td>Prostate</td>
<td>218 890</td>
<td>27 050</td>
</tr>
<tr>
<td>Skin (Non-melanoma)</td>
<td>&gt;1 000 000</td>
<td>&lt;2000</td>
</tr>
<tr>
<td>Thyroid</td>
<td>33 550</td>
<td>1530</td>
</tr>
</tbody>
</table>

2 Role of ABC Transporters

Cancer chemotherapy is the treatment of choice in many malignant diseases.
A major form of resistance against a variety of the antineoplastic agents
currently used involves the function of a group of membrane proteins that
extrude cytotoxic molecules, thus keeping intracellular drug concentration
below a cell-killing threshold. Multidrug transporters belong to the super-