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ORIGINAL ARTICLE

Synthesis, physicochemical and kinetic studies of redox derivative of bis(2-chloroethylamine) as alkylating cytotoxic agent for brain delivery

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Abstract Nitrogen mustard (mustine) containing an established anticancer moiety (N,N-bis(2-chloroethyl)amino is the one of the most active and widely used alkylating anticancer agents but it is too polar to cross the blood–brain barrier. The present study evaluates the utility of the dihydropyridine↔pyridinium salt redox system for the specific delivery and sustained release of bis-(2-chloroethyl)amine as anticancer moiety to the brain as an initial effort in a search for agents that may prove effective as CNS antitumor agent. The cytotoxic moiety bis-(2-chloroethyl)amine was converted into the corresponding 1-methyl-3-[bis-(2′-chloroethyl)amino]carbamoyl-1,4 dihydropyridine (**CDS-mustard**) (**4**), in three steps. Structures of all the synthesized compounds were characterized by UV, IR and ^{1}H NMR and ^{13}C NMR spectroscopic studies. *In vitro* chemical oxidation studies with silver nitrate of CDS-mustard indicated that it can be readily converted into its corresponding salt (**3**). *In vitro* kinetic studies of CDS-mustard showed that its rate of oxidation followed pseudo-first-order kinetics with reasonable half-lives in biological media. The study of some other physicochemical parameter calculated by online software also indicates that it can be a potential CNS antitumor agent.

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1. Introduction

Primary and secondary metastatic tumors of the CNS represent a major health problem globally. They are the second leading cause of cancer death in male adults aged 20–29 and the fifth leading cause of cancer death in female adults aged 20–39. Male are affected more than females. More than 200,000 people in the United States are estimated to be diagnosed with a primary or metastatic brain tumor (Jemal et al., 2010). Still, where possible, surgery remains the pre-

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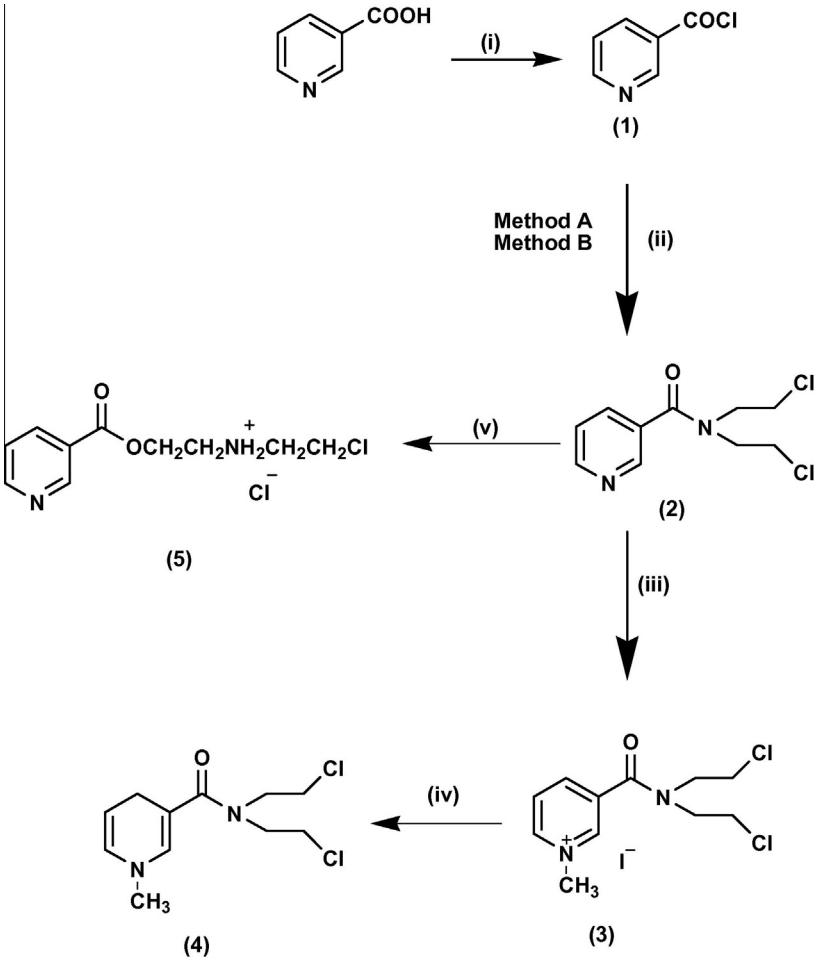
ferred method of treatment for most brain tumors and is often performed in conjunction with chemotherapy. But chemotherapy by antineoplastic agents is a challenge in the treatment of brain tumor. Many potential useful drugs including those active against peripheral tumors such as chlorambucil and melphalan due to their hydrophilicity cannot enter the brain and are therefore ineffective in treating cerebral neoplasms. The major obstruction to CNS drug delivery is the blood–brain barrier, which limits the access of drugs to the brain substance. The BBB comprises the endothelial lining of the microvessels in the brain, pericytes and astrocytes, and is the main barrier to drug transport into the CNS especially for labile hydrophilic compounds. In fact, it is estimated that only about 2% of potential CNS compounds can penetrate the BBB (Ambrose and Sheng-He, 2005).

Various attempts have been made to overcome the limited access of anticancer agent into the brain by synthesizing the lipophilic analogs of alkylating anticancer agent (Genka et al., 1993) or by linking the active anticancer moiety to lipophilic carrier (Peng et al., 1975; Bartzatt, 2004).

One of the most promising approaches for brain delivery is the concept of brain-specific drug delivery system based on a redox system analogous to the endogenous $NADH \leftrightarrow NAD^+$ coenzyme system developed by Bodor et al. (1981). The dihydropyridine↔quaternary salt redox system based chemical delivery system (CDS) has been investigated extensively as a method to enhance the selective delivery of drugs to the brain (Prokai et al., 2000). After entry into the brain, the CDS moiety is oxidized to a polar pyridinium species that cannot egress from the brain which then undergoes ester or amide cleavage to release the active drug and trigonelline.

This redox delivery system was successfully applied for brain-specific delivery of various alkylating anticancer agents. Chlorambucil (chlorambucil–CDH) (Bodor et al., 1989) and 1-(2-chloroethyl)3-cyclohexyl-1-nitrosourea (CCNU–CDH) (Raghavan et al., 1987) have been investigated to provide improved brain delivery relative to the parent compounds chlorambucil and CCNU, respectively. This system has also successfully been utilized to deliver nitrogen mustard group to the brain with ethyl as spacer group with promising results (EI-Sherbeny et al., 2003). Clearly there is a great need to develop therapeutic strategies that will provide efficient anticancer drug delivery to brain tumors. So it was therefore of interest to synthesize redox derivative of bis-(2-chloroethyl)amine (normustard) as alkylating anticancer moiety to the Bodor CDS directly, without any spacer group to evaluate its efficacy as a CNS anticancer agent by the given synthetic Scheme 1.



Scheme 1 Reagents and conditions: (i) Thionyl chloride; (ii) *Method A*: diethanolamine, thionyl chloride), *Method B*: bis(2-chloroethylamine; (iii) methyl iodide, acetone; (iv) sodium bicarbonate, sodium dithionite; (v) Trace amount of moisture, rearrangement.