Arabian Journal of Chemistry (2014) **xxx**, xxx–xxx

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Design, synthesis, chemical and biological evaluation of brain targeted alkylating agent using reversible redox prodrug approach

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Received 4 December 2012; accepted 10 December 2013

KEYWORDS

Alkylating agent;
Blood–brain barrier;
Redox system;
ADME;
NBP assay;
Biological oxidation

Abstract The aim of the present work is to investigate the utility of redox chemical delivery prodrug approach for the targeted and sustained release of an alkylating anticancer agent in the brain. The *N*-methyl-1,4-dihydronicotinate ester of an alkylating nitrogen mustard **NM-CDS (4)** was synthesized in three step reactions. Structures of all the synthesized compounds were confirmed by UV, IR, (^{1}H&^{13}C) NMR and CHN elemental studies. *In vitro* chemical oxidation studies with silver nitrate of **NM-CDS** (4) indicated that it can be readily converted into its corresponding quaternary salt (3) with half life of 8 min. *In vitro* biological oxidation studies showed facile oxidation in biological media and rate of oxidation followed pseudo first-order kinetics with reasonable half-lives of 32.5 min in rat blood, 24.2 min in human blood and 19.4 min in brain homogenate. The *in vivo* studies on Sprague–Dawley rats were performed. The **NM-CDS** (4) at a dose of 40 mg/kg, was injected into rats. At selected time intervals, blood samples and the brains were collected and analyzed by UV spectrophotometer. The results demonstrated that **NM-CDS** (4) was able to cross the blood–brain barrier (BBB) at detectable concentration, oxidized to its active quaternary salt **(Q-salt)** (3) and sustained there for some period of time. The *in silico* ADME descriptors required for CNS activity were determined by computational, online (Molinspiration) and QikProp 3.2 software

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Peer review under responsibility of King Saud University.

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http://dx.doi.org/10.1016/j.arabjc.2013.12.008

Please cite this article in press as: Singh, R.K. et al., Design, synthesis, chemical and biological evaluation of brain targeted alkylating agent using reversible redox prodrug approach. Arabian Journal of Chemistry (2014), http://dx.doi.org/10.1016/j.arabjc.2013.12.008

(Schrodinger, USA) that further indicated that **NM-CDS** (4) has a good potential to cross the BBB and show CNS antitumor activity.

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1. Introduction

The design of drugs for the chemotherapy of tumors of the CNS contains numerous challenges. A major difficulty in treating CNS tumors is the drug delivery into the CNS. One of the major obstacles is the blood–brain barrier (BBB) which is a primary reason for the non-penetration of drugs. The BBB, which restricts the delivery of drugs to the brain, is an uninterrupted monolayer of tightly connected endothelial cells covering the luminal surface of cerebral vasculature. Among the most frequently encountered anticancer drugs, nitrogen mustard (N-mustard) drugs such as chlorambucil, melphalan and mechlorethamine have been widely utilized in cancer chemotherapy (Francisco et al., 2008). These alkylating mustard derivatives exert their cytotoxic effects by interstrand cross-linking of DNA *via* aziridine formation and hence prevent DNA replication and cell death. Despite their strong antitumor activity, the clinical usefulness of nitrogen mustards has been restricted due to their non site-specificity, poor physicochemical properties and high chemical reactivity causing toxicity to normal tissues (Denny, 2008). Therefore, the search for novel nitrogen mustard agents devoid of these side effects continues to be an active area of research in medicinal chemistry and various modifications have been carried out in the last decade (Kapuriya et al., 2011; Leiris et al., 2010; Li et al., 2013; Mourelatos et al., 2012; Scutaru et al., 2011). They have been used clinically for various types of cancer including cervix, breast and prostate cancer. The possibility of extending their use to CNS tumor is limited by the fact that, it is highly hydrophilic and so cannot permeate the BBB. Thus designing and synthesizing CNS-directed alkylators have been one of the attractive approaches in the development of potent CNS anticancer agents (Bartzatt, 2004; Genka et al., 1993; Peng et al., 1975).

One of the most promising approaches for brain delivery is the prodrug concept of brain-specific chemical drug delivery system (CDS) based on redox system analogous to the endogenous NADH $\leftrightarrow$ NAD^+ coenzyme system developed by Bodor et al. (1981). According to this, polar drug linked to a lipophilic 1,4-dihydropyridine carrier could easily penetrate the BBB. After entry into the brain, this dihydro derivative is oxidized by (NAD $\leftrightarrow$ NADH) redox system to a polar pyridinium salt that cannot egress from the brain which then undergoes ester or amide cleavage to release the active drug and trigonelline. This redox system based chemical delivery system (CDS) has been the focus of CNS drug delivery efforts owing to evidence of its role to enhance the selective and sustain delivery of various anticancer agents to the brain (Bodor et al., 1989; El-Sherbeny et al., 2003; Prokai et al., 2000; Raghavan et al., 1987; Singh et al., 2012a, 2012b, 2013a, 2013b). CDS of estradiol have advanced to the Phase II clinical trials for the treatment of postmenopausal syndrome (Tapfer et al., 2004; Sziraki et al., 2006).

In our earlier study, we have synthesized and studied various redox derivatives of nitrogen mustard but compounds formed were not much stable when stored at room temperature (Singh et al., 2012b, 2013a). Therefore, there is a need to design more stable brain targeted nitrogen mustard with CNS active pharmacokinetic properties.

In the continuation of our work for the synthesis of CNS active agents (Singh et al., 2011, 2012a, 2012b, 2012c, 2013a, 2013b, 2013c, 2013d), in the present work, we extended our study to explore chemical delivery system approaches for alkylating agent to design and synthesize **NM-CDS** (4) to improve permeability of nicotinic-mustard **(NM)** alkylating agent across the brain (Fig. 1). This CDS of nicotinic-mustard **(NM)** being lipophilic, is supposed to be entered into the brain and oxidized into quaternary salt (3). The formed quaternary salt being hydrophilic is not effluxed from the brain and exerted its anticancer activity via aziridinium ion formation as shown in Fig. 2.

2. Experimental section

2.1. Chemistry

The melting points were determined on Veego-programmable melting point apparatus (microprocessor based) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker Avance-II, 400 MHz spectrometer and are reported in parts per million (ppm), downfield from tetramethylsilane (TMS) as internal standard. IR spectra were recorded on Perkin Elmer model 1600 FT-IR RX-I spectrometer as KBr disks. The ultraviolet spectra were recorded on Shimadzu, UV-1800 spectrophotometer. Elemental analyses for CHN were performed on Thermo-flash EA-1112 CHNS-O analyzer.

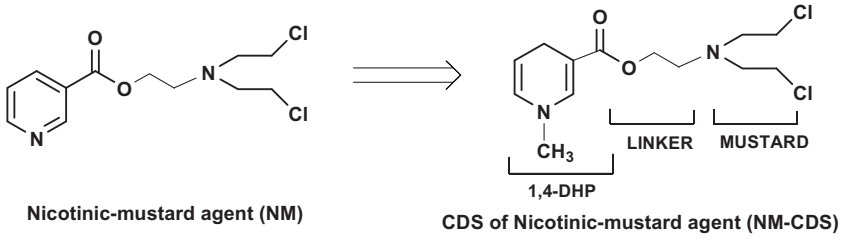

Figure 1 Design of redox derivative of nicotinic-mustard NM-CDS (4).

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