International Journal of Advanced Technology in Engineering and Science
Volume No.07, Issue No. 11, November 2019
www.ijates.com
ijates
ISSN 2348 - 7550

SYNTHESIS AND STUDIES OF REVERSIBLE REDOX CHEMICAL DELIVERY SYSTEM OF NITROGEN MUSTARD ANTICANCER AGENT

"1-methyl-3-[bis(2-chloroethyl)amino]carbamoyl-1,4-dihydro- pyridine"

Singh A, Singh N, Ratra M. and Singh J.

VMS College of Pharmacy, Batala, Distt- Guraspur, Punjab-143505

E-mail: singhamarjit201313@gmail.com

The present study evaluates the utility of the dihydropyridine↔pyridinium salt redox system for the specific delivery and sustained release of a bis-(2-chloromethyl)amine as anticancer moiety to the brain as the initial effort in a search for agents that may prove effective as CNS antitumour agent. The cytotoxic moiety bis-(2-chloromethyl)amine which is one of the most active and widely used alkylating anticancer agent was converted to the corresponding 1-methyl-3-[bis-(2′-chloromethyl)amino]carbamoyl-1,4 dihydropyridine **(3),** in three steps. The Bis-(2′-chloromethyl)amino-nicotinamide **(1)**, obtained by reaction of bis-(2-chloromethyl)amine hydrochloride with nicotinic acid in the presence of DMAP and DCC which was converted in quantitative yield to the 1-ethyl-3-[bis-(2′-chloromethyl)amino]carbamoyl-1,4-dihydropyridinium iodide on treatment with methyl iodide in acetone. Reduction of the latter with sodium dithionite gave the final compound, **(3)**. Structures of all the synthesized compounds were confirmed by U.V., IR, and ^{1}H NMR techniques. The *in-vitro* chemical oxidation studies data with silver nitrate and hydrogen peroxide by spectrophotometric techniques indicate that **(3)** has been converted into quaternary compound **(2)**. Hence it can be concluded that CDS of the nitrogen mustard alkylating agent has been developed. The study of some physicochemical properties calculated by online software such as lipophilicity, rule of five, number of NH or OH hydrogen bond donors, and nON value indicates that it can be a potential candidate for targeted and sustained delivery of anticancer agent to the brain for the treatment of brain tumour.

INTRODUCTION

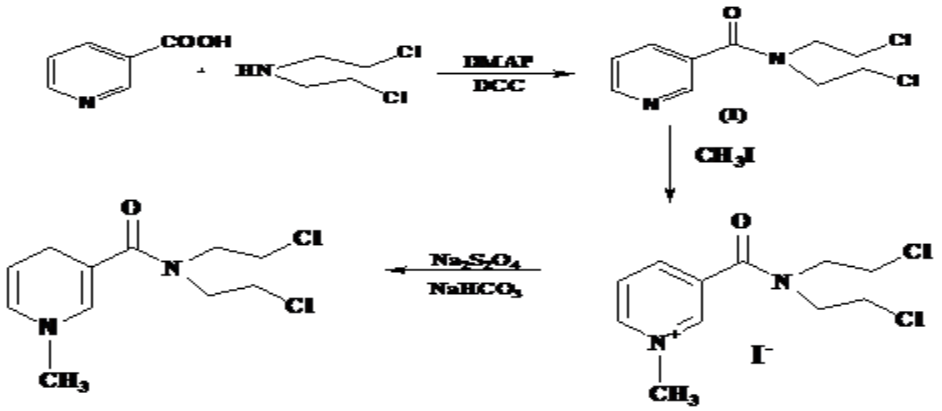
The site-specific and sustained release of drugs to the brain is both important and challenging[1]. Reversible redox drug delivery system represents novel and systematic ways of targeting active biological molecules to brain in which drug is chemically linked to nictotinic acid to form lipophilic 1, 4 dihydroform to produce dihydropyridine↔pyridinium ion type redox delivery system. After entry into brain, the CDS moiety is oxidized to a polar pyridinium species that cannot efflux from the brain which then undergoes amide cleavage to release the active drug and trigonelline[2].

OBJECTIVE

Nitrogen mustard is the one of the most active and widely used alkylating anticancer agents. But nitrogen mustard is too polar to cross the highly lipophilic BBB[3]
The present study evaluates the utility of the dihydropyridine↔pyridinium salt redox system for the specific delivery and sustained release of a bis-(2-chloroethyl)amine as anticancer moiety to the brain as the initial effort in a search for agents that may prove effective as CNS antitumour agent.

EXPERIMENTAL WORK

1) **Synthesis of Bis-(2/-chloroethyl)amino nicotinamide (1):-**
   To a pyridine solution containing N-bis(2-chloroethyl)amine hydrochloride and nicotinic acid at 0^0C was added DCC and DMAP and stirred the reaction mixture at room temperature for 24 hrs. Dicyclohexyl urea formed was filtered and residue was dissolved in ice-water to obtained crystal of **(1).**
2) **Synthesis of 1-methyl-3-[bis(2-chloroethyl)amino]carbamoyl-1,4-dihydro-pyridinium iodide (2):-**
   A mixture Bis-(2/-chloroethyl)amino nicotinamide **(1)** of and methyl iodide was dissolved in methanol, and refluxed for 5 hrs then stirred for 24 hrs. Solvent was removed under reduced pressure to get the desired compound **(2)**



3) 1-methyl-3-[bis(2-chloroethyl)amino]carbamoyl-1,4-dihydro- pyridine (3):-

To a solution of **(2)** in deaerated water add sodium bicarbonate and ether. The mixture was stirred in ice bath and sodium dithionite was added gradually over a period of 5 min. The mixture was stirred for 3 hrs under nitrogen. The ether layer was separated, washed, dried and evaporated to get yellow colour final compound **(3)**

Structures of all the synthesized compounds were confirmed by U.V., IR, ^{1}H NMR techniques

IN-VITRO CHEMICAL OXIDATION STUDIES:

Oxidation by Silver Nitrate. To **5** ml of saturated methanolic $AgNO_3$ solution was added 1 ml of 5% methanolic solution of the dihydropyridine derivative. The mixture was shaken, left for 5 min to complete oxidation , centrifuged, and an absorbance of the solution was determined and concentration was determined by standard curve.

Oxidation by Hydrogen Peroxide.

To 10 ml of 30% hydrogen peroxide was added 0.2 g of the dihydropyridine derivative. The mixture was stirred, and absorbance of the solution was determined and concentration was determined by standard curve.

From the above both results it was inferred that the compound (3) has been converted into quaternary compound (2). Hence it can be concluded that CDS of the nitrogen mustard alkylating agent has been developed.

PHYSICOCHEMICAL EVALUATION

Since target compound is designed to be CNS active, hence the parameter were selected which effect blood brain barrier. All the parameters were calculated by method of molinspiration. The miLogP value of bis(2-chloromethyl)amine is 0.958 and that of target compound is 1.706 that shows that lipophilicity of the CDS is much superior to those of the parent drug. The target compound shows zero number of violations of rule of five which shows good bioavailability and bioactivity and has no NH or OH hydrogen bond donors which show increase solubility in cellular membranes. The target compound has nON value 3 which is <10 and has molecular weight 245.621 which is <500 preferable for compound to be CNS active. All this properties could permit a better penetration of the drug through the blood-brain barrier.

CONCLUSION

Reversible redox chemical delivery system for nitrogen mustard has been successfully synthesized and characterized. Upon oxidation, it gave the quaternary ion form. The study of some physicochemical properties indicates that it can be a potential candidate for targeted and sustained delivery of anticancer agent to the brain for the treatment of brain tumour.

REFERENCES

1. Pardridge W M*; Jour. Amer. Soc. Exp. NeuroTherap.,* 2(1), 1, 2005
2. Prokai L, Prokai-tartrai K, Bodor N; *Med. Res. Rev*., 20 (5), 367, 2000.
3. Hirata T and Driscol J S; *J Med. Chem*., 65 (11), 1699, 1976

--------x--------