A Review on Nitrogen Mustards: "Key Players in the Fight Against Cancer

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Abstract— Among alkylating agents, nitrogen mustards are the most commonly utilized .Only five of the thousands of nitrogen mustards that has been created and tested are currently often utilized in cancer treatment - Melphalan, Cyclophosphamide, Ifosfamide, Chlorambucil and Mechlorethamine-the classic 'nitogen mustards'-are among them. Every nitrogen mustard undergoes a reaction via an aziridinium intermediate, and the bis-chloroethyl group is the distinctive chemical component of nitrogen mustards. The rest of the molecule has an impact on the transport, distribution, and reactivity of the particular agents and is crucial in establishing the molecule's physical characteristics.

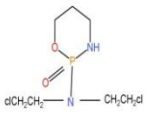
Keywords:-Nitrogen mustard, cancer, alkylation, DNA damage

I. INTRODUCTION

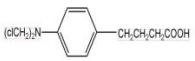
The term ''cancer''describes any of a wide range of illnesses marked by the growth of aberrant cells that divide uncontrolled and have the capacity to invade and kill healthy bodily tissue. Cancer is the second most leading disease in the world.

Regarding Alkylating compounds have been used to treat cancer for more than 60 years, and their application is growing. These chemicals have a direct impact on DNA at all phases of the cell cycle. They disrupt DNA strands, crosslink N-7-guanine residues, cause abnormal base pairing, stop cell division, and eventually kill cells. The main focus is on finding ways to improve the therapeutic efficacy of alkylating drugs by combining them with other anticancer medicines or by inhibiting DNA repair enzymes, topoisomerases, COX-2, p34cdc2 kinase, phosphatases, multi-drug resistance proteins, and anti-vascular agents.

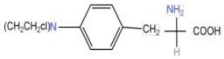
Among the DNA alkylating chemicals most frequently utilized in cancer chemotherapy are nitrogen mustards (Povirk LF, 1994) .Despite not being a reactive substance, cyclophosphamide is activated in body. One structural isomer of cyclophosphamide is isofosfamide is specifically used to treat sarcomas and testicular cancers (Antman KH, 1990) . Melphalan is an alkylating agent that is used in the treatment of multiple myeloma, (Costa G, 1973) ovarian cancer (Young RC, 1990)and breast cancer (Fisher B, 1979) (Rivkin SE, 1989).Chlorambucil is used for the treatment of chronic lymphocytic leukemia (Rundles RW, 1959) .ovarian carcinoma, (Harding M, 1988) (E., 1965) and lymphoma, (Galton DA, 1955) (Portlock CS, 1987) ,but has been utilized less frequently than the other nitrogen mustards in high-dose combination treatments.



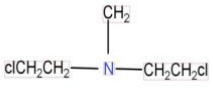
CYCLOPHOSPHAMIDE



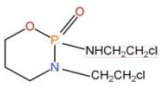
CHLORAMBUCIL



MELPHALAN

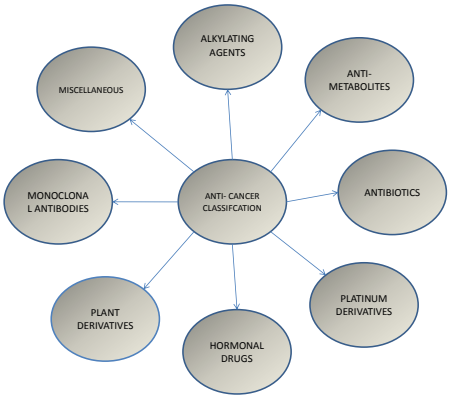


MECHLORETHAMINE



IFOSFAMIDE

II. CLASSIFICATION OF ANTI-CANCER DRUGS



III. GENERAL SYNTHESIS

1.AMINATION:-

A primary amine reacts with ethyleneoxide or ethanolamine to produce a hydroxyl functionalized amine.

$R\text{-}NH_2 + CH_2CH_2OH \longrightarrow R\text{-}NHCH_2CH_2OH$

2.CHLORINATION

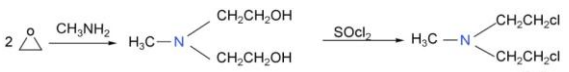
The hydroxyl groups are converted to chlorides using thiony chloride ($socl_2$),yielding the nitrogen mustard derivative.

$R\text{-}NHCH_2CH_2OH + SOCl_2 \longrightarrow R\text{-}N(CH_2CH_2Cl)_2$

IV. SYNTHESIS OF THE DRUGS OF NITROGEN MUSTARDS

MECHLORETHAMINE

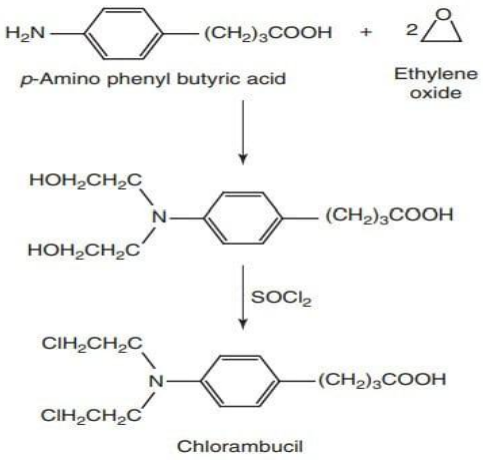
Mechlorethamine, also known as bis-(2-chloroethyl) methylamine, is created when ethylene oxide and methylamine mix to yield bis-(2-hydroxyethyl)methylamine, which then reacts with thionyl chloride to produce the required mechlorethamine.



Ethylene oxide Mechlorethamine

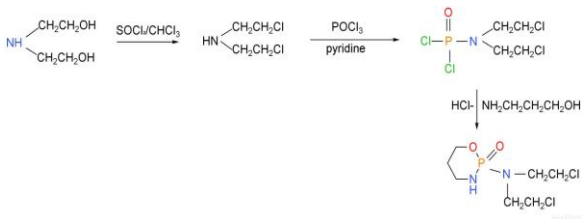
CHLORAMBUCIL

Chlorambucil, 4-(p-(bis-(2-chloroethyl)amino) phenyl)butyric acid ,is made from p-amino phenyl butyric acid and ethylene oxide.



CYCLOPHOSPHAMIDE

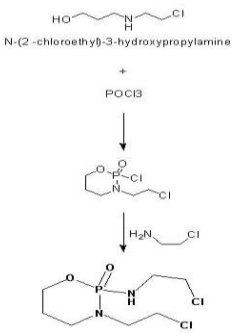
When bis(2-chloroethy)amine and phosphorous oxychloride react, N,N-bis-(2-chloroethyl) dichlorophosphoramide is produced. This is then converted to cyclophosphamide,2-(bis-(2-chloroethyl)amino)tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide."



cyclophosphamide

IFOSFAMIDE

Ifosfamide, 3-(2-chloroethyl)-2-[(2-chloroethyl) amino]tetrahydro-2H-1,3,2 oxaphosphorin-2-oxide,which is viewed as an isomeric compound of cyclophosphamide. It is made by reacting N-(2-chloroethyl)-N-(3-hydroxy propyl amine with phosphorous oxychloride giving 3-(2-chloroethyl)-2-chlorotetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide,which is reacted with N-(2-chloroethyl)amine, forming the desired ifosfamide.



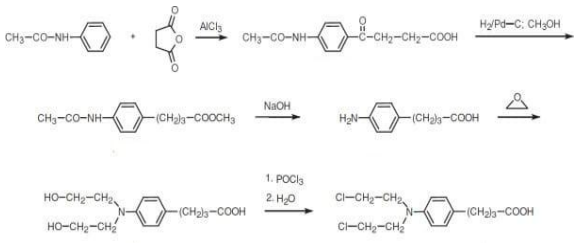
ifosfamide

MELPHALAN

Melphalan,1-3-[p-[bis-(2-chloroethyl) amino] phenyl] alanine, is a structural analogue of chlorambucil.

When this reacts with ethanol in the presence of hydrogen chloride, 4-nitro-1-phenyl alanine ethyl ester is converted to hydro chloride. The amino group of this ester is shielded by a reaction with succinic anhydride, which converts it to phthalamide.

Using palladium on calcium carbonate as a catalyst, the nitro group in this molecule is converted to an amino group. Abis-(2-hydroxyethyl)-amino derivative is the outcome of the reaction between the aromatic amine and ethylene oxide. This molecule's hydroxyl group is changed to chlorine atoms when it reacts with thionyl chloride. The phthalimide protection is then removed by hydrochloric acid treatment, resulting in melphalan.



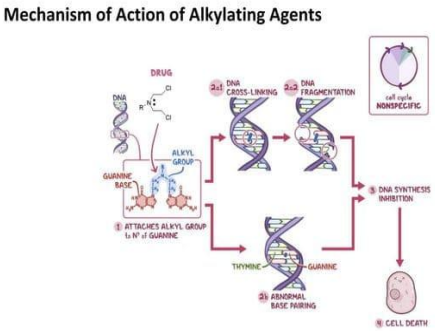
V. MECHANISM

1.DNA ALKYLATION

- Alkylating agents covalently bind to nucleophilic sites on DNA, particularly at the N7 position of guanine and other nitrogen or oxygen atoms in bases, such as the N3 position of adenine or the O6 position of guanine (Chabner BA, 2011).
- This alkylation can result in the formation of monoadducts, cross-links, or DNA strand breaks.

2.INDUCING OF DNA STRAND BREAKS

- If alkylation is not repaired, it can result in single-and double- strand breaks.
- These DNA breaks activate the p53 pathway, leading to cell cycle arrest at the G2/M checkpoint (DeVita VT, 2010).



VI. STRUCTURE ACTIVITY RELATIONSHIP

The scientific term “structure activity relationship” (SAR) refers to the connection between a molecule’s chemical or three – dimensional structure and its biological activity. It is mostly utilized in medicinal chemistry and drug creation. The SAR aids researchers in comprehending how a compound’s efficacy, potency, selectivity, and toxicity might be affected by various chemical alterations.

ELECTRON WITHDRAWING GROUPS

The presence of electron withdrawing groups has a major impact on nitrogen mustard action. Electron withdrawing groups typically reduce the nitrogen atom nucleophilicity when they are included into the structure of nitrogen mustards. These chemicals alkylating activity may decline as a result of this decrease in nucleophilicity (Chen W, 2014).

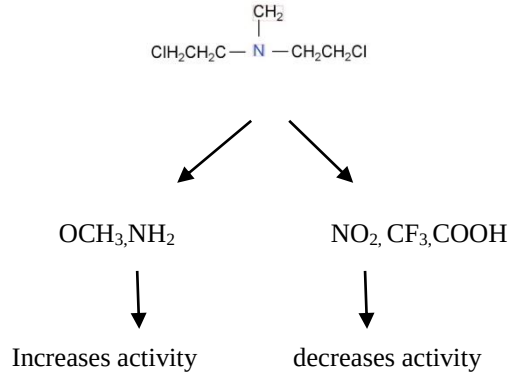
The aromatic nitrogen mustard can be deactivated with an electron withdrawing linker unit, such as a quaternary ammonia salt, a carboxamide carbonate group, resulting in less than 1.5%cross linking formation.

ELECTRON DONATING GROUPS

Electron –donating groups increase the electron density on the nitrogen atom of nitrogen mustards, making them more nucleophilic. This can enhance their reactivity towards electrophiles, including DNA.

Electron donating groups have the potential to improve therapeutic results by increasing nitrogen mustards selectivity against cancer cells.

EG: MECHLOETHAMINE



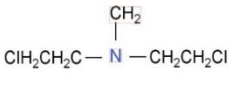
ALKYL CHAINLENGTH

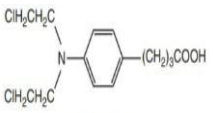
Alkyl chain lengthening increases cytotoxicity,but too much length decreases activity.

ARYLSUBSTITUTION

Aryl groups (like phenyl) at the R position increases activity presumably because they better attach to DNA.

Example: chlorambucil is more active than mechlorethamine due to presence of the phenyl group.





MECHLORETHAMINE CHLORAMBUCIL

HALOGENS

Alkylating activity is increased by the presence of chlorine or bromine the CH_2CH_2Cl location. (LS., 1996) (WO., 2008).

PRESENCE OF HETEROCYCLIC RING

In biological system, nitrogen mustard stability and solubility may be impacted by the addition of heterocyclic rings. This absorption, distribution, metabolism, and excretion (ADME) pharmacokinetics may be affected.

REPLACEMENT OF NITROGEN

The ability of the chemical to produce these intermediates can be diminished by substituting other atoms (suchas carbon, phosphorus,or sulphur) for nitrogen.

VII.ACKNOWLEDGEMENTS

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VIII.CONCLUSION

In this review we covered the drugs regarding anti-cancer, belonging to the class of nitrogen mustards. Nitrogen mustards are cytotoxic alkylating agents characterized by their chloroethyl amine functional group. By the presence of the electron donating groups and aryl groups the activity of the compound gets increased. The compounds are used in the treatment of various evil diseases. These Nitrogen mustards are effective against malignant lymphoma. Their mechanism involves DNA alkylation, leading to cell death. Despite being relatively easy to synthesize novel methods of synthesis must be developed in upcoming generation.

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