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Chemical Inhibition Of Integrase Enzyme Of Hiv

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Abstract

HIV (human immunodeficiency virus) involves the presence of three enzymes in its life cycle:, viz Viral protease, reverse transcriptase, and Integrase. We have focused our study on inhibition of integrase enzyme, as its mutagenic tendencies are very low. Here we have synthesized drug molecules which have two pronged actions, one complexation of Mg2+ or Mn2+ ions with drug molecules as these ions act as cofactors for integrase enzymes, and the second action as regards to binding of drug molecules with human DNA, leading to conformational and configurational changes in it; thus, it becomes difficult for the viral DNA to integrate with human DNA.

KEYWORDS: Mutagenic, Enzyme Cofactor , Conformational changes, Configurational changes

INTRODUCTION:

HIV is an example of retro virus which when infects human body reduce the immunity of the body mediated through action on helper T cells, macrophages and dendritic cells. Incubation period of this infection from HIV is large and ultimately with this reduced immunity can lead to drug resistant TB ,cancers etc. There are almost over 45 million people who are infected with HIV in world and over 20 millions are from African countries.

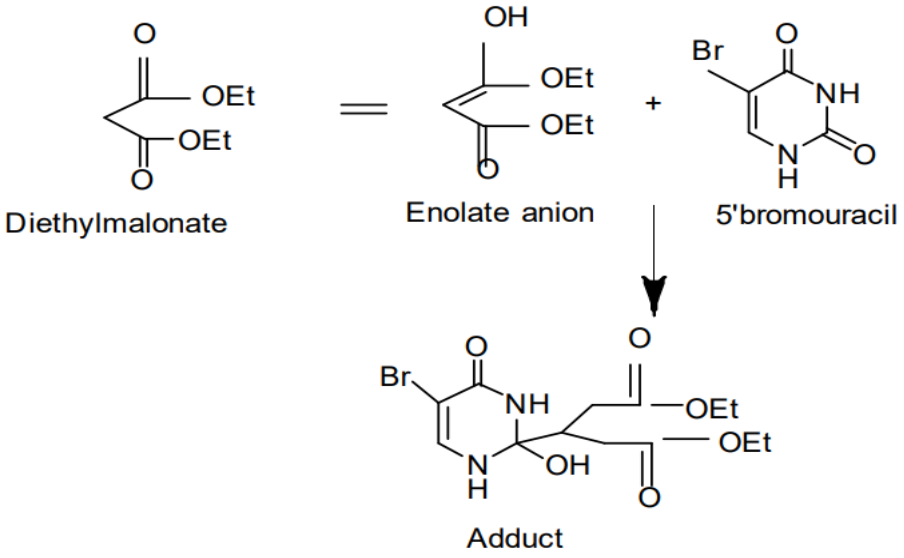
RESEARCH METHODOLOGY:

The Integrase enzyme of HIV comes to the essential task of transferring virally coded DNA to human DNA. It has a high therapeutic effect,, i.e. large amounts of drugs may be administered to obtain the desired effect of inhibition of the integrase enzyme of HIV. The active site of the enzyme, in particular, involves three negatively charged amino acids (acidic amino acids), which form the core of the enzyme. This core is stabilized by either Mg2+ or Mn2+ ions. This active site involves the presence of β pleated and α helix structures, and structures of the latter ease the conformational changes of the core site suitable for 3' processing. The first line of defense mechanism against

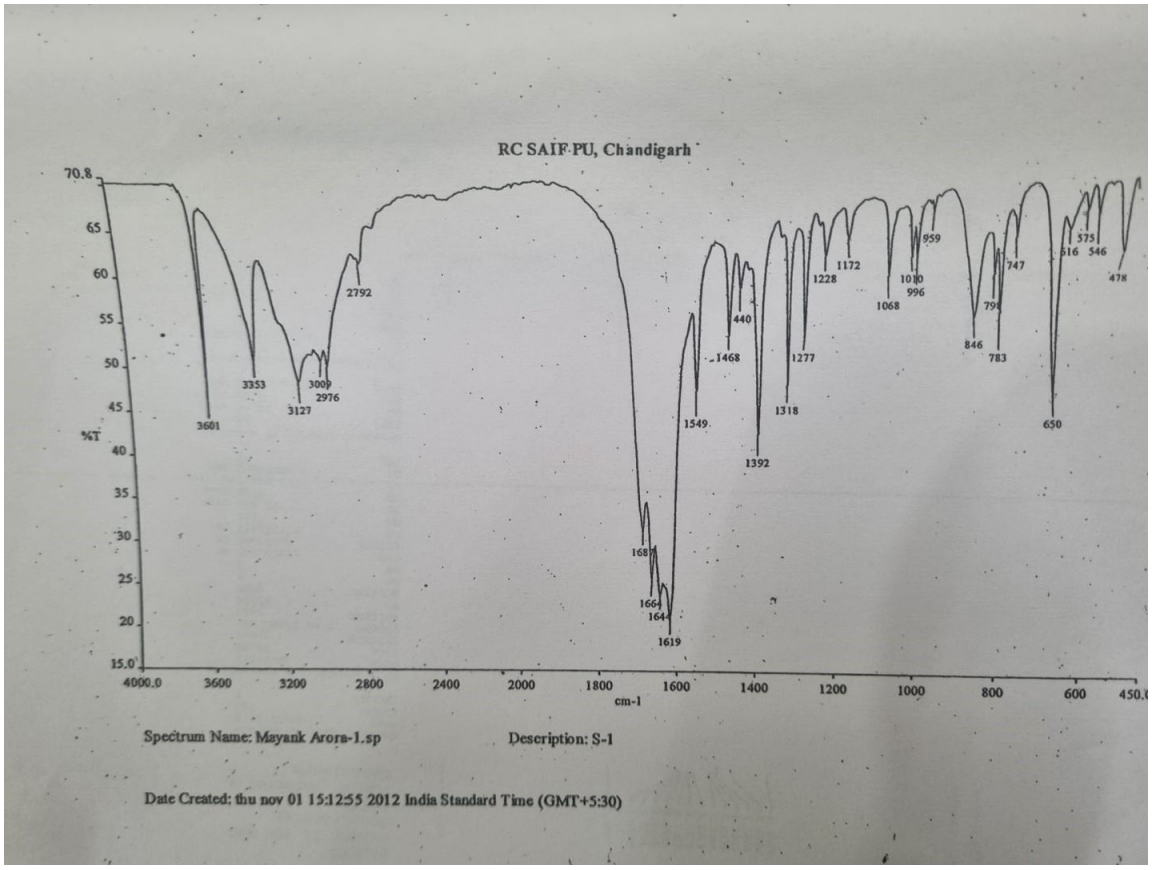
viruses involves substitution of the core amino acid sequence, while the second line of defense mechanism involves chelation of Mg2+ and Mn2+ ions with drug molecules that also retard the activity of an enzyme. HIV integration involves first 3' processing, where viral integrase loops down to bind the short sequence of nucleotides lying near the 3' ends of both DNA. Then ligation of viral DNA to human DNA involves direct attack of OH functionality present at the 3' end as nucleophile into phosphodiester backbone of human DNA. Afterward there takes place lysis of one or two nucleotides from 5' end of viral DNA that leaves gap between viral DNA and human DNA. There are several domains of amino acids other than active site of enzyme which shows due role in integration of viral DNA to human DNA. One primary target involves chelation of drug molecules which act as multi dentate ligand e.g. The N terminal domain involves the presence of S containing amino acids like cysteine, and we know that sulfur shows great affinity for oxygen, so drug molecules involving the presence of naked oxygen as a ligand may prove useful in inhibition.

RESEARCH WORK:

A reaction was carried out between diethymalonate and 5' bromouracil in the presence of base ethoxide. The concentration of base is maintained such that one mole of enolate ions is produced.



Now, as we examine the pyrimidine character in 5'-bromouracil, we find that it has functionalities like carbonyl groups and imine links, which are highly e-withdrawn groups, so this type of structure is facilitated by nucleophilic attack at positions 2, 4, and 6. Position 5 is relatively e-rich. Further hydrolysis of ester functionality was not carried out in order to mask Mg2+ ions and simultaneously to prove our adduct molecule as a folly nucleotide. The IR spectra support the structure as prominent peaks for free OH functionality at 3601 cm1, the –NH stretch peak at 3353 cm1, the C=C peak at 1640 cm-1 and the presence of the –C=O peak at 1680 cm-1 confirm the structure. Furthermore, according to NMR spectra, the peak at δ 2.5 confirms the presence of a C-H bond in which the C atom is attached to a highly e-withdrawn group. A converging multiplet between δ values between 3.2 to 5 shows the presence of the N-H bond and the O-H bond, respectively. Then the peak between 7 and 8 indicates the presence of hydrogen atoms that are linked to a highly conjugative C chain.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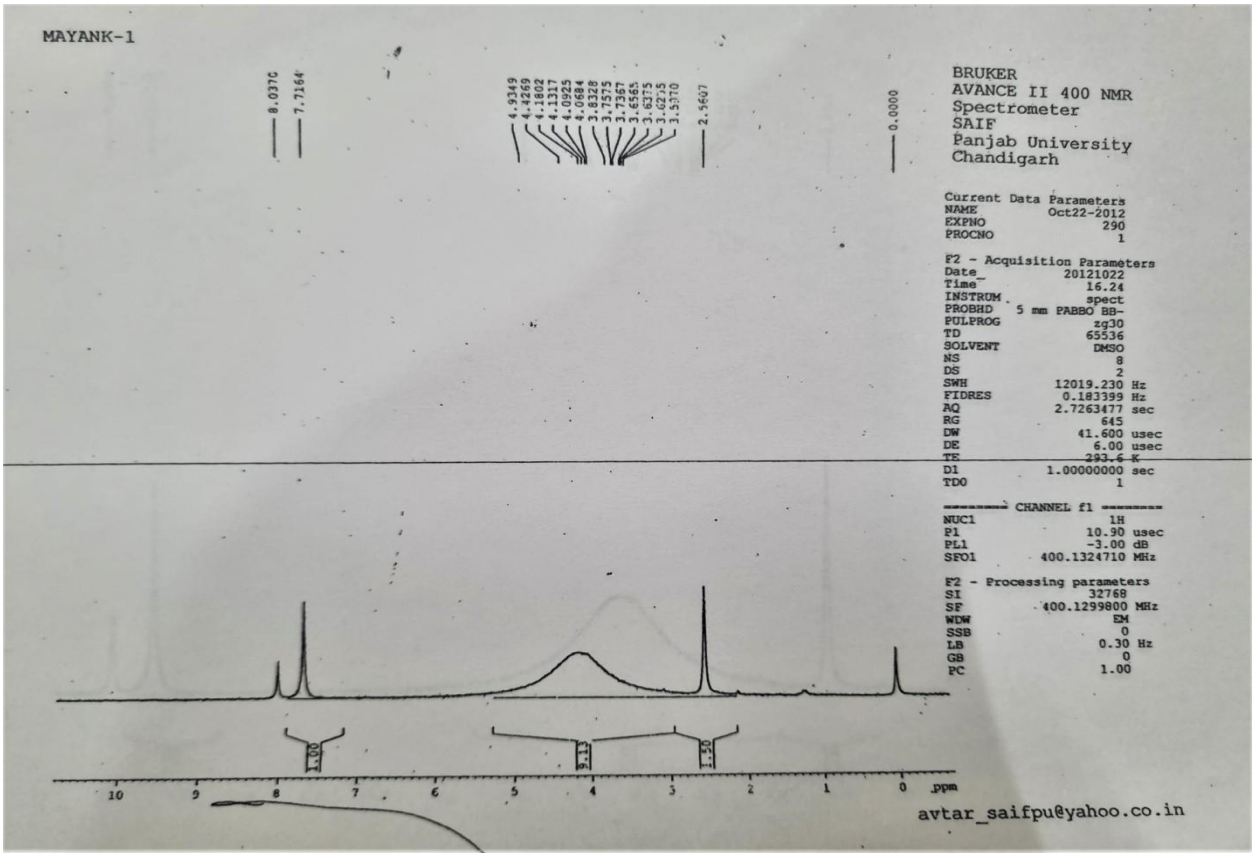
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BRUKER
AVANCE II 400 NMR
Spectrometer
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Panjab University
Chandigarh
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RESULTS:

The tendency of this adduct to form complexes with Mg2+ ions was studied by carrying out complexometric titration. For this purpose, an N\10 MgSO4 was prepared. This solution was titrated against the N/10 EDTA (Ethylenediaminetetraacetato ion) solution. Obviously, 10 ml of the latter was used till the end point of titration was reached, i.e., when all the magnesium ions present in 10 ml of N/10 solution formed a 1:1 complex with EDTA molecules. There was clear indication of binding of adduct molecules with Mg2+ ions as on introduction of 0.02 gm of the former, the volume of EDTA solution consumed to titrate 10 ml of N/10 MgSO4 solution was reduced to only 4 ml till the end point. Thus, quantitatively, the initial concentration of Mg2+ ions in 10 ml of N/10 MgSO4 solution = 10/10000 = 0.001 gm. equivalent Concentration of Mg2+ ions left after administering 0.02 gm in 10 ml of N/10 solution = 4/10000 = 0.004 gm equivalent. Thus, %age binding per 0.02 gm. of adduct compound = 0.0006 × 100/0.001= 60%
2) The oligomer with composition 5'AAGTTCAAGCTTTGCAATTG gives a blue color with diphenylamine, but on introduction of 0.1 mg of drug adduct, the color of the solution becomes yellow, indicating high binding affinity of it with DNA. This will reduce the binding affinity of viral DNA with human DNA both through conformational and configurational changes in it.

CONCLUSION:

Here we have contributed towards formation of an adduct molecule to inhibit the integrase enzyme of HIV both through masking Mg2+ or Mn2+ ions and through producing conformational and configurational changes in DNA which inhibit integration of viral DNA with human DNA.

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