03. X–12 INTERCALATING AGENTS.

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Several molecules are well known to interact with nucleic acids by intercalation between paires of bases. Some of them, like ellipticine derivatives, have antitumoral activity, some other like, psoralen derivatives, have photosensitizing activity.

X-Ray analysis of such molecules has been undertaken to increase the knowledge either, of the stacking possibilities between rings and bases or, of the precise geometry of photoproducts after irradiation. In this case, synthetic models were used (Ade-chain-Pso or Thy-chain-pso).

The collected results allow to suggest a possible mecanism of photocyclisation when nucleic acids are irradiated in presence of psoralen derivatives.

03. X–13 STRUCTURAL STUDIES OF LEDAKRIN AND ITS ANALOGUES. Andrzej Ledochowski, Maria Bogucka-Ledochowska, Jenny P. Glusker and John J. Stezowski, Department of Pharmaceutical Technology and Biochemistry, The Technical University, 80-952 Gdansk, Poland; The Institute for Cancer Research, The Fox Chase Cancer Center, Philadelphia, PA 19111, U.S.A.; Universität Stuttgart, Stuttgart 80, Federal Republic of Germany.

The specificity of acridines for tissues has long been known and various modifications have been effective as mutagens, carcinogens and antitumor agents. The introduction of a 1-nitro group into the acridine nucleus gives a compound, ledakrin (nitracrine), that has been successfully used as an antitumor agent in humans in Poland. The structures of ledakrin [9-(3-dimethylaminopropylimino)-1-nitro-9,10-dihydroacridine, C-283] and several analogs have been determined by X-ray crystallographic techniques and show that the 1-nitro group interferes sterically with the 9-substituted position, so causing buckling in the molecule. We present here data on such compounds as free bases or as acid salts; the type of distortions found in such 1-nitro compounds are discussed. Our studies suggest that the 1-nitro-9-amino substituents favor selection of the imino tautomeric form with a double bond from C(9) to the external 9-amino nitrogen atom. We propose that the imino tautomer for is important for antineoplastic activity. The results of docking these structures into a DNA (by computer graphics) will be discussed in light of the biological activities of these compounds.

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03. X–14 STRUCTURAL BASIS FOR DIHYDROFOLATE REDUCTASE INHIBITION. By David A. Matthews, Jesus E. Villafranca, and Joseph Kraut, Department of Chemistry, University of California, San Diego, La Jolla, California.

The effectiveness of the antifolates as chemotherapeutic agents against various bacterial and neoplastic diseases has spurred extensive research on dihydrofolate reductase (DHFR), the target enzyme, and on its interaction with these powerful inhibitors. As a result, abundant information has accumulated on DHFR including its three dimensional structure and a discription of its interaction with antifolate drugs at the molecular level Of particular interest to us has been the active-site interactions which account for the extremely tight binding of methotrexate, an inhibitor of DHFR which is in widespread clinical use. There is now strong evidence from x-ray diffraction (Matthews et.al., Science 197, 452-455 (1977)) and ^{13}C nuclear magnetic resonance studies (Cocco et.al., Arch. Biochem. Biophys. 226, 567-577 (1983)) that N1 of methotrexate (MTX) is protonated when bound to DHFR and that a charge interaction exists between an aspartate (bacterial) or a glutamate (vertebrate) in the enzyme and the protonated N1. The crystal structures of DHFR from E. coli and L. casei complexed with methotrexate have been refined to 1.7Å resolution and show, in great detail, the interactions between DHFR and MTX (Bolin et.al., J. Biol. Chem. 257, 13650-13662 (1982)). The refined structure gives support to the notion of a charge interaction between MTX-N1 and aspartate 27 (e.c.) and reveals that since methotrexate binds with the pteridine ring in a flipped orientation as compared with the substrate, dihydrofolate (DHF), an additional hydrogen bond forms at the 4-amino which cannot form for DHF. Although the significance of the ionic interaction in the DHFR:MTX complex has been generally recognized, recent evidence suggests that the additional hydrogen bond may contribute as much or more to MTX binding. Using oligonucleotide-directed mutagenesis, a mutant of E. coli DHFR has been constructed which has the aspartate at position 27 replaced by an arginine (Villafranca et.al., Science 222, 782-788 (1983)). The mutant DHFR shows no protonation of MTX in the binary complex but only a 100 fold lower binding constant for MTX than the wild type enzyme. This indicates that the charge interaction is probably not responsible for the entire 10^4 to 10^5 higher affinity DHFR has for methotrexate verses dihydrofolate.