03.4-2 STRUCTURAL STUDIES ON IMMUNO-MODULATORS. By T. Srikrishnan, Center for Crystallographic Research and Department of Biophysics, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, NY 14263, U.S.A.

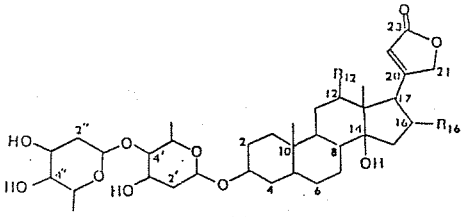
Immunomodulators are drugs that enhance or suppress immune response. Suppression of immune response is a requirement for the successful transplant of tissues and organs from genetically different sources. Enhancement of immune response is required in the treatment of tumors and use of vaccines. A variety of immunomodulators are used but so far no rationale has been provided as to how these agents work. An investigation of the crystal structures of these drugs is undertaken as a first step in the understanding of immunomodulators. Levamisole is a synthetic derivative of tetramisole that is widely used as an anthelmintic drug in humans and animals. In humans it restores delayed hypersensitivity reaction in cancer patients and is used in the treatment of breast cancer. Crystals of levamisole. HCl are orthorhombic, $P2_12_12_1$, a=5.915(1), b=12.934(1), c=14.690(1) Å, Z=4, D_m=1.42 g cm^{-3} CAD4 data, structure from MULTAN80, final R 0.027. The imidazolothiazole ring is planar and has a dihedral angle of 31° with respect to the phenyl ring. The nitrogen, N(1), of this ring is protonated and the crystal structure is stabilised by a N-H...Cl hydrogen bond. There is a short intermolecular S...Cl contact of 3.296 Å in the structure. Levamisole is supposed to function like imidazole in controlling cyclic nucleotide levels in lymphocytes that affect their function and induce immuno-regulation. Azimexon [2-cyanaziridinyl-2-carbamoyl-aziridinyl-1-propane] is an immuno-stimulant which shows therapeutic effects in tumor models, enhances T-lymphocyte transformation in vitro. In cancer patients it increases blood active T-rosettes, increases the T4/T8 ratio and is used in the treatment of melanoma. Crystals of Azimexon are triclinic, space group P1, with a=6.342(2), b=6.804(1), c=13.106(2) Å, α=75.17(1), β=89.17(2), γ=83.26(2)°, Z=2, D_m=1.18 g cm^{-3}, CAD4-data, structure from MULTAN80, final R 0.057. There are two azimexon molecules in the crystal structure which differ significantly in the relative orientation of their aziridine rings. The configuration of the ring nitrogen is pyramidal and the mean C-N and C-C bond lengths are 1.461 and 1.494 Å respectively. The molecules are linked by hydrogen bonds involving the amino group as donor and the cyano nitrogen and the carbonyl oxygen of the other molecule as acceptor. The aziridine rings are implicated in the immune response producing a T-cell enhancement. Perphenazine is used as an anti-emetic agent and is used in the treatment of psychotic disorders. Crystals of this drug are triclinic, space group P1 with a=8.131(1), b=11.880(8), c=12.109(8) Å, α=60.81(4), β=89.4(4), γ=89.9(4), Z=2, D_m=1.31 g cm^{-3}. Structural studies of this drug as well as Frentizole and trifluoperazine are in progress. Thanks to Boehringer Mannheim for the gift of the samples of azimexon. Work supported by ACS IN 54W8, N.Y. State Department of Health and in part by NIH GM-24864. Thanks are due to my summer students Tom Lou and Christopher Wood for taking part in these studies.

03.4-3 THE BIOSIDES OF DIGITALIS LANATA. By Kuantee Go and K. Bhandary, Center for Crystallographic Research and Department of Biophysics, Roswell Park Memorial Institute, Buffalo, New York 14263, U.S.A.

Several models have been proposed to describe the mechanism of action of cardiac glycosides on Na+, K+-ATPase (R. Thomas et al., Supp. I Circ. Res. 46, 167-172 (1980); K.R. Repke et al., Sci. Pharm. Proc., 1, 39-57 (1966)). The understanding of the conformation of cardiac glycosides is an important step towards the understanding of mechanism of its action. We have been studying the conformation of these glycosides in crystalline state using x-ray crystallographic techniques. As part of our project, we report here the results of our studies on the biosides of digitoxigenin 1, gitoxigenin 2 and digoxigenin 3 & 4. The feature of the steroid nucleus is similar except on the D-ring. The D-ring conformation of 1 is between a 13α, 14β half-chair; 2 is a 13β envelope; 3 is a distorted 15α envelope; 4 is a 14β,15β half-chair. The hydroxyls, the carbonyl and the solvents are involved in H-bonding which combined with the D-ring conformation seem to have an effect on the orientation of the lactone ring and the sugar.

Cell parameters of the biosides:

	1	2	3	4
a	11.447(1)	11.348(2)	35.715(6)	7.458(2)
b	14.304(1)	14.388(3)	14.442(4)	10.646(4)
c	23.985(3)	23.732(6)	7.526(1)	13.064(5)
α	90	90	90	104.78(3)
β	90	90	90	105.23(3)
γ	90	90	90	83.07(3)
S. G.	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	P1
R	0.077	0.085	0.093	0.066



*This work was supported by New York State Department of Health.