Summary

Although aziridinyl cyclophosphazenes have already been recognized as cytostatic agents for 25 years, various aspects of this biological activity are still hardly understood. This thesis describes a study of the relations between structure and cytostatic activity of this class of compounds.

The general introduction gives a treatment on aziridinyl cyclophosphazenes against the background of other cytostatic agents derived from aziridine (C_2H_4NH), *e.g.* Thiotepa and TEM. These compounds are to be considered as capable of alkylating certain biological substrates under physiological conditions. The resulting biological effects and possible action mechanisms are summarized in relation with the chemical structure.

Chapter II deals with the behaviour of aziridine in substitution reactions with $(NPCl_2)_3$. The various substitution stages show a partly geminal reaction pattern, which is very remarkable for a secondary amine. From the comparison with the closely related dimethylamine it appears that the stereoselectivity in corresponding reactions can be largely ascribed to the substituent solvating effect as defined by Goldschmidt. All possible isomers of the resulting products $N_3P_3Az_nCl_{6-n}$ (n = 1-6) could be isolated, mostly using HPLC techniques. From these compounds derivatives $N_3P_3Az_nR_{6-n}$ (n = 1-6; R = primary or secondary amino, ethylglycinato, 1-imidazolyl, alkoxy, aryloxy, aryl) were also synthesized in order to obtain analogous compounds for the biological screening. The reverse route *via* $N_3P_3R_nCl_{6-n}$ was also employed, drawing special attention to the sequence in reactivity of PAmCl centres in $N_3P_3Am_nCl_{6-n}$ (n = 1-3; Am = Pyr, Pip, Morph) towards aziridine: PPyrCl > PPipCl > PMorphCl.

The substitution pattern of the first three aziridinolysis steps of the eight-membered ring system $(NPCl_2)_4$ is described in Chapter III. In this case again partly geminal substitution takes place. A comparison with the observations described in the previous chapter reveals clear simi-

larities in the stereoselectivity of the aziridinolysis of $(NPCl_2)_3$ and $(NPCl_2)_4$. For the first time the isolation of complete series of isomers $N_4P_4Az_2Cl_6$ and $N_4P_4Az_3Cl_5$ is realized by improved (HPLC) separation techniques. The conversion of $N_4P_4Az_nCl_{8-n}$ into $N_4P_4Az_nAm_{8-n}$ (n = 1,2; Am = NHMe, NMe_2) results in compounds with possibly interesting cytostatic properties.

Chapter IV presents a survey of the ^{31}P-, ^{13}C-, and ^{1}H NMR spectra of the compounds prepared and deals with the trends present in the NMR parameters. The analysis of the NMR spectra of the various isomeric bis-, tris-, and tetrakisaziridinyl derivatives of both the trimer and the tetramer leads to unambiguous structure assignments. The *trans* conformation of two key compounds, *viz.* *trans*-$N_3P_3Az_2Cl_4$ and 1,*trans*-3-$N_4P_4Az_2Cl_6$, determined by means of X-ray diffraction, is in agreement with the NMR data.

The investigation of the cytostatic activity of the aziridinyl cyclophosphazenes prepared, described in Chapter V, shows similar results in two different *in vitro* screening systems. The determination of the 50% inhibition dose (ID_{50}) in L1210 mouse leukaemia cells and of the lowest active dose (LAD) in L5178Y mouse lymphoma cells gives insight into activating and deactivating structural features. Apart from the presence of aziridinyl groups, electron-donating substituents in the N-P ring system appear to be essential for effective tumour growth inhibition. Hydrolytic instability leads to loss of activity. Furthermore, the results indicate that the number of active centres (= PAz_2 or PAzR) in the molecule, required to attain a high cytostatic activity, should be at least two. *In vivo* the compounds are also active, referring to the chemotherapeutic effect of a selected number of compounds against leukaemia L1210 in mice. This is expressed as the ratio of the life-span of treated *versus* untreated (control) animals (= T/C %). Finally, the structure-activity relations observed are worked out into proposals for further studies.