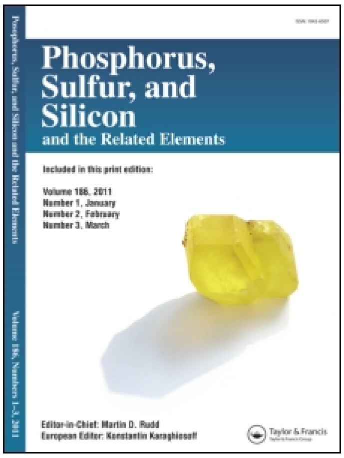

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

New designs and structure activity relationships in antitumoral aziridinyl cyclophospha(thia)zenes

J. C. Van De Grampel[a]; A. A. Van Der Huizen[a]; A. P. Jekel[a]; J. W. Rusch[a]; T. Wilting[a]; W. Akkerman[b]; P. Lelieveld[b]; H. B. Lamberts[c]; A. Van Der Meer-Kalverkamp[c]; N. H. Mulder[d]; S. Rodenhuis[d]
[a] Departments of Inorganic Chemistry, University of Groningen Rijswijk, AG Groningen, The Netherlands [b] Department of Inorganic Chemistry, University of Groningen Rijswijk, AG Groningen, The Netherlands [c] Radiopathology, AG Groningen, The Netherlands [d] Division of Medical Oncology, AG Groningen, The Netherlands

To cite this Article Van De Grampel, J. C. , Van Der Huizen, A. A. , Jekel, A. P. , Rusch, J. W. , Wilting, T. , Akkerman, W. , Lelieveld, P. , Lamberts, H. B. , Van Der Meer-Kalverkamp, A. , Mulder, N. H. and Rodenhuis, S.(1983) 'New designs and structure activity relationships in antitumoral aziridinyl cyclophospha(thia)zenes', Phosphorus, Sulfur, and Silicon and the Related Elements, 18: 1, 337 — 340

To link to this Article: DOI: 10.1080/03086648308076034

URL: http://dx.doi.org/10.1080/03086648308076034

Phosphorus and Sulfur, 1983, Vol. 18 pp. 337-340
0308-664X/83/1801-0337/$18.50/0

NEW DESIGNS AND STRUCTURE ACTIVITY RELATIONSHIPS IN ANTITUMORAL AZIRIDINYL CYCLOPHOSPHA(THIA)ZENES.

J.C. VAN DE GRAMPEL[a], A.A. VAN DER HUIZEN[a], A.P. JEKEL[a], J.W. RUSCH[a], T. WILTING[a], W. AKKERMAN[b], P. LELIEVELD[b], H.B. LAMBERTS[c], A. VAN DER MEER-KALVERKAMP[c], N.H. MULDER[d], AND S. RODENHUIS[d].
Departments of Inorganic Chemistry[a] and Radiopathology[c], University of Groningen, Division of Medical Oncology[d], University Hospital Groningen, and Radiobiological Institute TNO[b] Rijswijk. Postal adress: Department of Inorganic Chemistry, Nijenborgh 16, 9747 AG Groningen, The Netherlands.

Abstract The partial aziridinolysis of $(NPCl_2)_{3,4}$ and $(NPCl_2)_2NSOCl$ yields non-geminal and geminal chloro-aziridinyl derivatives. Compounds $N_3P_3Az_{6-n}R_n$ (R=amino, alkoxy, aryloxy, id.) show in vitro and in vivo cytostatic activity. Structure-activity relationships are proposed. Phase I clinical trials of $(NPAz_2)_2NSOAz$ (Az=1-aziridinyl) are summarized.

SYNTHESIS

A detailed investigation of the substitution pattern of aziridine with $(NPCl_2)_3$ by ^{31}P NMR revealed that the generally accepted view of a merely geminal substitution pathway had to be revised[1]. Reactions with molar ratio $(NPCl_2)_3$: aziridine = 1 : 4 in the solvents diethyl ether and benzene showed that geminal and non-geminal (*cis*,*trans*) bis(1-aziridinyl) derivatives are formed in about equal quantities. Since compounds $N_3P_3Cl_3Az_3$ are also formed, the ratio of isomers $N_3P_3Cl_4Az_2$ is influenced by their different reactivities towards further chlorine substitution (sequence of reactivity: *trans*-$N_3P_3Cl_4Az_2$ > *cis*-$N_3P_3Cl_4Az_2$ > *gem*-$N_3P_3Cl_4Az_2$). The relatively high yield of *cis*-$N_3P_3Cl_4Az_2$ demonstrates that the non-geminal diaminolysis of $(NPCl_2)_3$ by aziridine does not show the well-known *trans* isomer preference. The formation of *gem*-$N_3P_3Cl_4Az_2$ leads to the conclusion that a nucleophilic attack at the PClAz centre can compete successfully with a reaction at PCl_2. The geminal substitution predominates when the degree of aminolysis increases, e.g. at the tetrakis stage *gem*-$N_3P_3Cl_2Az_4$ is the major reaction product.

The introduction of a second aziridinyl group into the tetramer $(NPCl_2)_4$ gave an abundance of the non-geminal isomers $N_4P_4Cl_6Az_2$ (ratio non-geminal/geminal ≈ 20). The predominance of the non-geminal bis(aziridinyl) derivatives can be explained from the higher reactivity of the tetrameric system.

In the case of the sulfur-containing system $(NPCl_2)_2NSOCl$ only unstable products were formed. Although no derivatives have been isolated, ^{31}P NMR data of the reaction mixtures clearly pointed to both geminal and non-geminal substitution of chlorine atoms by aziridinyl groupings.

The systems $N_3P_3Az_{6-n}R_n$, $N_4P_4Az_{8-n}R_n$ and $N_2P_2Az_{4-n}R_nNSOX$ (X = F,Ph,Az) were used as suitable models for investigating substituent effects on antitumoral properties. Compounds were obtained either by a primary reaction with aziridine and further substitution by R or by the reverse route.

ANTITUMOR ACTIVITY

Tumor cell growth inhibition *in vitro* was measured in two different screening systems: the determination of the 50% growth inhibition dose (ID50) in a leukaemia L1210 clonogenic assay and the determination of the lowest active dose (LAD) in mouse lymphoma L5178 Y cells[2]. As an *in vivo* screening the prolonging of the lifetime of L1210-bearing mice was used, expressed as T/C values (mean lifetime treated/mean lifetime control %). Over sixty compounds have been investigated *in vitro*, whereas for a limited number *in vivo* studies were carried out.

Evaluation of the *in vitro* data of compounds $N_3P_3Az_{6-n}R_n$ showed the following factors to promote the activity:

a. The presence of electron releasing substituents R.

b. Hydrolytic stability.

c. The presence of aziridinyl groups on at least two different P-atoms in the ring system.

Both item a and b are illustrated by the *in vitro* screening results of compounds $N_3P_3Az_5R$ and *gem*-$N_3P_3Az_4R_2$. By increasing the electron donating capacity of R, expressed by the substituent constant α_R, the ID50 (L1210) and LAD (L5178 Y) values (in 10^{-6} mol L^{-1}) decrease. Hydrolytically unstable compounds like the glycino ethyl ester derivatives are less active than might be expected from the value of α_R[3]. Comparison of the screening data of isomeric compounds $N_3P_3Az_2R_4$ [R = NHMe, Pyr (= 1-pyrrolidinyl), Morph (= 4-morpholinyl)] leads to the third conclusion, as the non-geminal isomers are more active than their geminal forms, e.g. *cis*- and *trans*-$N_3P_3Az_2(NHMe)_4$: mean ID50 (L1210) = 4.2, mean LAD (lymphoma L5178 Y) = 1.3; *gem*-$N_3P_3Az_2(NHMe)_4$:ID50 = 27.8, LAD = 8. The compounds $N_3P_3Az(NHMe)_5$ and $N_3P_3AzMorph_5$ may be considered as inactive, $N_3P_3AzPyr_5$ only shows a weak activity.

The screening of the tetrameric analogs $N_4P_4Az_2R_6$ is underway. In the group of cyclophosphathiazenes the pentakis(aziridinyl) derivative $(NPAz_2)_2NSOAz$ appears most promising. Replacement of one of the aziridinyl residues at phosphorus does not affect the *in vitro* activity significantly. Variation of the S-bonded groups seems to exert a larger effect.

In general, *in vitro* data seem to correlate well with preliminary *in vivo* results, which suggests that the compounds investigated have not to be metabolized to some active form.

PHASE I CLINICAL TRIAL

Based on the favourable results in *in vivo* experiments[4], the compound $(NPAz_2)_2NSOAz$ (code name SOAz) was selected for phase I clinical trials. In a first trial 31 patients with advanced cancer were treated by intravenous infusion on days 1,2,3 and 4 of a 21-

day cycle, occasionally postponed to allow for hematological recovery. The clinical study showed that SOAz causes myelosuppression, especially thrombocytopenia. This toxicity appeared to be cumulative and dose-limiting. In three cases irreversible effects were observed. The highest tolerated dose for patients who had received no or only minor previous chemotherapy was 300 mgm^{-2}, for heavily pretreated patients 175 mgm^{-2}. Concerning the antitumor activity no responses were observed[5].

In a second phase I trial, involving 11 patients, SOAz was administered by i.v. infusion once a week. Analogous toxicity effects were observed as described above. Two minor responses took place, which might indicate that SOAz has antitumor activity on human level. This encourages the search for related compounds, which may combine useful clinical activity with acceptable toxicity.

REFERENCES

1. A.A. van der Huizen, A.P. Jekel, J. Rusch and J.C. van de Grampel, Recl. Trav. Chim. Pays-Bas, 100, 343 (1981).
2. H.B. Lamberts, A. van der Meer-Kalverkamp, J.C. van de Grampel, A.A. van der Huizen, A.P. Jekel and N.H. Mulder, Oncology, 40, 301 (1983).
3. A.A. van der Huizen, J.C. van de Grampel, W. Akkerman, P. Lelieveld, A. van der Meer-Kalverkamp and H.B. Lamberts, Inorg. Chim. Acta, 78, 239 (1983).
4. J.F. Labarre, F. Sournies, S. Cros, G. François, J.C. van de Grampel and A.A. van der Huizen, Cancer Letters, 12, 245 (1981).
5. S. Rodenhuis, N.H. Mulder, D.Th. Sleijfer, H. Schraffordt Koops and J.C. van de Grampel, Cancer Chemoth. Pharmacol., 10, 178 (1983).