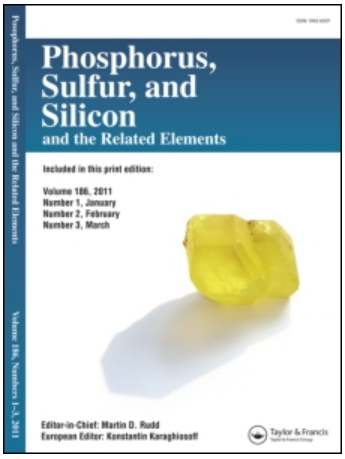

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Photobiology and Photodynamic Activity of Selenium-Containing Cyanine and Oxonol Dyes

Marianne Krieg

To cite this Article Krieg, Marianne(1998) 'Photobiology and Photodynamic Activity of Selenium-Containing Cyanine and Oxonol Dyes', Phosphorus, Sulfur, and Silicon and the Related Elements, 136: 1, 357 — 360
To link to this Article: DOI: 10.1080/10426509808545961
URL: http://dx.doi.org/10.1080/10426509808545961

Phosphorus Sulphur and Silicon
Vols. 136, 137 & 138 pp. 357–360
Reprints available directly from the publisher
Photocopying permitted by license only

PHOTOBIOLOGY AND PHOTODYNAMIC ACTIVITY OF SELENIUM-CONTAINING CYANINE AND OXONOL DYES

MARIANNE KRIEG
Spectra Science Corporation, 56 Amaral Street,
East Providence, RI 02915, USA

Structure-activity studies with chemically modified cyanine dyes revealed that the photophysics and photodynamic activity of these dyes could be significantly improved by strategically positioning heavy atoms into the chromophore structure. Based on these studies, trimethine oxonol dyes with superior light-induced antineoplastic properties were developed and their photodynamic potential was assessed and confirmed in a pre-clinical evaluation.

Keywords: cyanine dyes; oxonol dyes; photophysics; cancer; photodynamic therapy

INTRODUCTION

During the past decade, cyanine dyes have gained interest as potential future photodynamic and photochemotherapeutic agents. Merocyanine 540 (MC540), the best known photosensitizer from this dye family, effectively sensitizes the photoinactivation of leukemia, lymphoma and neuroblastoma cells but is rather ineffective in removing most solid tumor cells as well as normal hematopoietic stem cells[1]. This preference for specific neoplastic cells is currently exploited in a phase I/II clinical trial for the extracorporeal purging of autologous bone marrow grafts. From a photophysical viewpoint,

however, the observed high antineoplastic activity of MC540 is unexpected: MC540 has rather modest photophysical properties in terms of quantum yields of triplet formation and cytotoxic singlet molecular oxygen generation[2]. Clearly, there is potential to develop cyanine dyes with improved antineoplastic properties by optimizing the photophysics through strategic structural modifications.

RESULTS AND DISCUSSION

Comparative photophysical and photobiological investigations with a variety of N-alkyl carbocyanine dyes and MC540 analogues (Fig. 1) have shown that increasing the size of heteroatoms located in

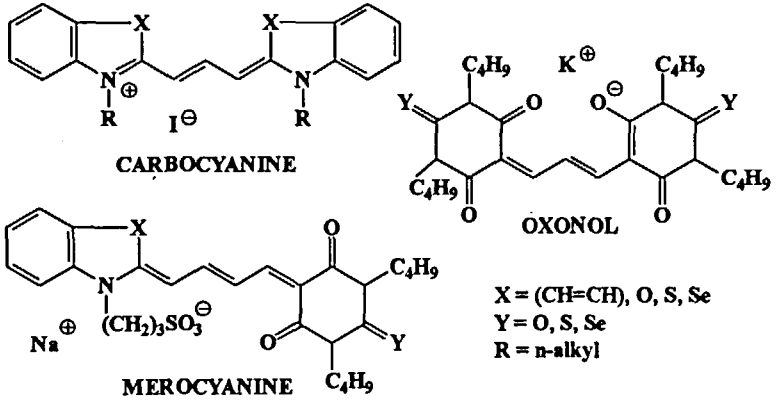

FIGURE 1. Chemical structures.

position X and Y in the chromophore strongly influenced the photophysics as well as the photodynamic activity of such dyes[3,4]. This chemical modification, which induced an internal heavy atom effect, caused an increase in triplet state formation and singlet oxygen production. As a consequence, the selenium analogues had consistently superior photodynamic properties than the corresponding oxygen and sulfur derivatives. The extent of the internal heavy atom effect, however, was strongly dependent on the position of the modified heteroatom. The replacement of the two benzothiazole groups of a trimethine carbocyanine dye with benzselenazole moieties enhanced singlet oxygen formation 15-fold

and caused a two-fold increase in antineoplastic activity. The improvement, however, appeared to be rather modest. By comparison, exchanging the heteroatom Y on position 2 of the barbituric acid had a significantly larger impact, e.g., the selenium analogue of MC540 (X = O, Y = Se; Fig. 1) had a 160 times larger singlet oxygen quantum yield than the corresponding sulfur derivative MC540 (X = O, Y = S; Fig. 1) and it experienced a 33-fold increase in photodynamic activity.

Taken together, these results strongly suggest that the photophysics and photodynamic activity could be further improved by replacing the "inactive" chalcogenazole moiety of a merocyanine dye with a second "active" thiobarbituric or selenobarbituric acid group. Photophysical and photobiological experiments confirmed that both these trimethine oxonol dyes (Y = S, Se; Fig. 1) had indeed superior antineoplastic properties. In addition, the selenium oxonol derivative was identified, as expected, as the most potent dye of all polymethine dyes explored in these studies. A pre-clinical evaluation of these oxonol dyes revealed that the induced photodynamic damage was selective: under conditions where > 5 log L1210 or HL60 leukemia cells were inactivated, hematopoietic stem cell toxicity was ≤ 2 log[5]. Additional *in vivo* experiments simulating an autologous bone marrow transplantation confirmed the selectivity of oxonol-induced photodamage. As Fig. 2 shows, when heavily irradiated mice were transplanted with a mixture of $5x10^6$ syngeneic marrow cells containing $5x10^4$ L1210 leukemia cells (line 2), all animals died of leukemia after a median survival time of 26 days. By contrast, when the same cell mixture was exposed to

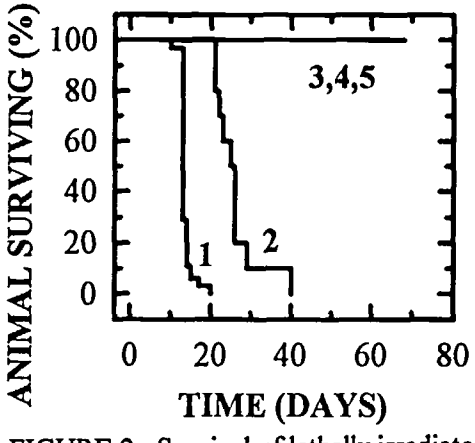

FIGURE 2. Survival of lethally irradiated (11 Gy) B6D2F1/J mice receiving simulated autologous bone marrow grafts. Each group consisted of ≥ 10 animals.

5 μM selenium oxonol dye and visible light of 4 or 8 kJ/m^2 before implantation (lines **3** and **4**, respectively), all transplanted animals survived a ≥ 70-day observation period (Fig. 2: lines **1** and **5** are additional control groups; **1**, mice received no graft; **5**, mice received untreated 5x10^6 syngeneic marrow cells).

A pre-clinical evaluation also revealed that both the sulfur and selenium oxonol dye retained, in contrast to the previously studied cyanine dyes, their photodynamic efficacy against a wide range of solid tumor cells. Although all solid tumor cell lines tested (A549 and LL/2 lung carcinoma; MDA-MB-468 breast adenocarcinoma and MMT mammary tumor; U373 glioblastoma and Daoy medulloblastoma) were less sensitive to oxonol sensitization than leukemia cells, a ≥ 5 log depletion was readily achieved by increasing the light dose 2-3 fold. Furthermore, these oxonol dyes were found to be effective against multidrug-resistant neoplastic cell lines. For example, multidrug-resistant P388/ADR leukemia cells were as effectively eliminated as cells of the corresponding P388D1 wild type line.

The results from these pre-clinical studies suggest that oxonol dyes may be potentially useful for the purging of leukemia as well as breast cancer cells from autologous bone marrow grafts. In addition, these studies support our previous observation that photophysical data obtained in solution may be valuable tools for pre-screening and estimating the photodynamic effectiveness of photosensitizing dyes.

Acknowledgments

This work was supported by grant CA50733 from the National Cancer Institute and the MACC Fund.

References

[1.] F. Sieber, *J. Hematother.*, **2**, 43-62 (1993).

[2.] P.F. Aramendia, M. Krieg, C. Nitsch, E. Bittersmann and S.E. Braslavsky, *Photochem. Photobiol.*, **48**, 187-194 (1988).

[3.] M. Krieg, J.M. Bilitz, M.B. Srichai and R.W. Redmond, *Biochim. Biophys. Acta,* **1199**, 149-156 (1994).

[4.] R.W. Redmond, M.B. Srichai, J.M. Bilitz, D.D. Schlomer and M. Krieg, *Photochem. Photobiol.*, **60**, 348-355(1994).

[5.] M. Krieg, J.M. Bilitz, D.L. Traul and F. Sieber, *Cancer Research, Therapy and Control,* **4**, 163-172 (1995).