Progress in Drug Research

Fortschritte der Arzneimittelforschung

Progrès des recherches pharmaceutiques

Editor:
Ernst Jucker

36

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Foreword

Volume 36 of "Progress in Drug Research" contains 5 articles and the various indexes which facilitate its use and establish the connection with the previous volumes. While all articles deal with some of the topical aspects of drug research, the contribution by Robert R. Ruffolo *et al.* on "Drug receptors and control of the cardiovascular system: Recent advances" is indeed in its own right a monographic presentation of this important domain.

The remaining four reviews provide an overview of the work involved in the search for new and better medicines, with a focus on chemical, pharmacological, toxicological, biological, biochemical and molecular modeling studies.

In the 31 years this series has existed, the Editor has enjoyed the help and advice of many colleagues. Readers, the authors of the individual articles, and, last but not least, the reviewers have all contributed greatly to the success of PDR. Although many comments received have been favorable, it is nevertheless necessary to analyze and to reconsider the current position and the direction of such a series. So far, it has been the Editor's aim to help spread information on the vast domain of drug research, and to provide the reader with a tool helping him or her to keep abreast of the latest developments and trends. The reviews in PDR are useful to the non-specialists who can obtain an overview of a particular research field in a relatively short time. The specialist readers of PDR will appreciate the reviews' comprehensive bibliographies. Moreover they may even get fresh impulses for their own studies. Finally, all scientists interested in drug research can use the 36 volumes of PDR as an encyclopedic source of information.

It gives me great pleasure to present this new volume to our readers. At the same time, I would like to express my gratitude to Birkhäuser Verlag and, in particular, to Mrs. L. Koechlin and Mssrs. H.-P. Thür and A. Gomm. Without their personal commitment and assistance, editing PDR would be a nearly impossible task.

Basel, April 1991 Dr. E. JUCKER

Vorwort

Der vorliegende, 36. Band der «Fortschritte der Arzneimittelforschung» enthält fünf Artikel sowie die verschiedenen Register, welche das Arbeiten mit dieser Reihe erleichtern. Alle Referate behandeln aktuelle Gebiete der pharmazeutischen Forschung; der Beitrag von R. Ruffolo vermittelt gar eine geradezu monographische Übersicht über die Kontrolle des kardiovaskulären Systems mit Hilfe von Arzneimittel-Rezeptoren. In allen Beiträgen werden die Aspekte der Chemie, Biochemie, Biologie, Pharmakologie und Toxikologie berücksichtigt.

Seit der Gründung der Reihe sind 31 Jahre vergangen, und der Herausgeber konnte stets auf den Rat der Fachkollegen, der Leser und Autoren zählen. Ihnen allen möchte ich auch hier meinen Dank abstatten. In diesen Dank sind auch die Rezensenten eingeschlossen, denn sie haben mit ihrer Kritik und ihren Vorschlägen wesentlich zum guten Gedeihen der Reihe beigetragen. Viele Kommentare waren positiv und lobend. Trotzdem ist es angebracht, die Frage nach dem Sinn und Zweck der «Fortschritte» zu stellen und zu überprüfen.

Nach wie vor ist es unser Ziel, neueste Forschungsergebnisse in Form von Übersichten darzustellen und dem Leser auf diese Weise zu ermöglichen, sich rasch und mühelos über bestimmte Gebiete und Richtungen zu informieren. Es wird ihm somit die Möglichkeit gegeben, sich in diesem komplexen Forschungsgebiet auf dem laufenden zu halten und den Kontakt zum Fortschritt in diversen Teilbereichen nicht zu verlieren. Die Übersichtsreferate der «Fortschritte» bieten einerseits dem aktiven Forscher, der ja meistens in einem relativ engen Gebiet tätig ist, nützliche Vergleichsmöglichkeiten, andererseits stellen sie für den Spezialisten eine wertvolle Quelle der Originalliteratur dar. So kann dieser rasch feststellen, ob er in seiner Literaturrecherche alle wichtigen Publikationen erfaßt hat.

Zum Gelingen dieses Werkes haben nicht zuletzt auch die Mitarbeiter des Birkhäuser Verlages, vor allem Frau L. Koechlin und die Herren H.-P. Thür und A. Gomm, wesentlich beigetragen. Auch ihnen möchte ich an dieser Stelle meinen Dank aussprechen.

Basel, April 1991 Dr. E. JUCKER

Pharmacology of synthetic organic selenium compounds

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1 Introduction

The similarity in the chemical properties of sulfur and selenium has tempted medical chemists for many years to prepare, for comparative purposes, a wide variety of selenium derivatives of sulphur- or oxygen-containing compounds. Because of the widespread use of this chemical comparison, the list of published and/or patented structures of organic selenium compounds is extensive. Two detailed, but rather uncritical, reviews of organic selenium compounds synthesized as possible drugs have been written in the past, by Klayman in 1973 [1] and by Shamberger in 1983 [2]. Many of the compounds reviewed were synthesized, however, as part of a chemical series and were never studied for biological activity beyond initial screening. Other compounds had similar activities to the parent sulfur- or oxygen-containing analogues and therefore offered no pharmacological advantage. With the discovery of the essential role of selenium in the active center of the enzyme glutathione peroxidase [3] and the increasing understanding of the physiological importance of selenium in the regulation of oxidative damage [4,5], interest has grown in the synthesis of organic compounds on the basis of the biological and chemical properties of their selenium moieties rather than as analogues of known compounds.

In this chapter we shall concentrate on synthetic organic selenium compounds which have been subjected to more than just a biological screen, with the emphasis being laid on studies carried out recently, subsequent to the review of Shamberger [2]. Selenoamino acids are not discussed because their pharmacological activities can not clearly be distinguished from their nutritional properties for which they are frequently compared with inorganic selenium.

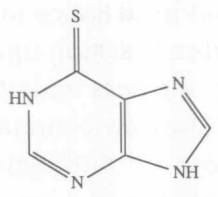
2 Anti-cancer compounds

Despite early concerns about the carcinogenicity of selenium, no evidence exists for such effects at nutritionally acceptable doses in man [6] and considerable debate has been raging in recent years over the anticarcinogenic activity of selenium [7–11]. This debate has stimulated the search for anti-cancer agents with low toxicity.

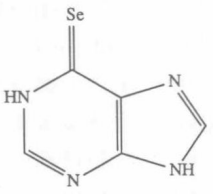
2.1 Selenopurines

The sulfur-containing purines were initially studied in the 1940's by Hitchings and ultimately led to his share in a Nobel prize in 1988. Mercaptopurine and thioguanine (Table 1) are the major representatives of this class of antimetabolites which act by inhibiting purine ring biosynthesis and nucleotide interconversions during nucleic acid

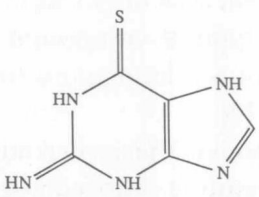
Table 1
Purines and selenopurines with anti-neoplastic activity



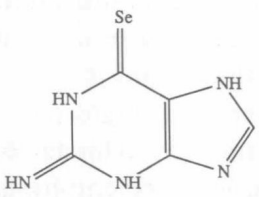
6-mercaptopurine



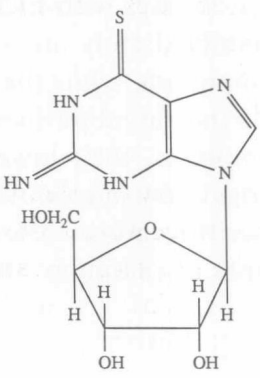
6-selenopurine



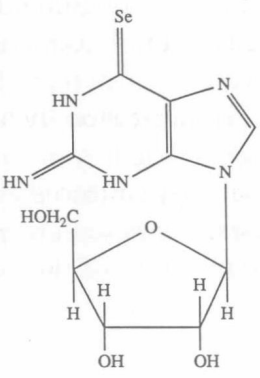
6-thioguanine



6-selenoguanine



6-thioguanosine



6-selenoguanosine

synthesis. Mautner and his colleagues [12, 13] first synthesized the selenium analogues of mercaptopurine and thioguanine (Table 1) in the late 1950's and early 1960's, to investigate the effect of the different electron distribution around the selenium atom on the properties of the compounds. As reviewed by Shamberger [2], both these compounds were widely tested and shown to exhibit antitumor activities *in vitro* and *in vivo* against leukemia L5178Y, sarcoma 180 and Ehrlich ascites tumors in mice. However, 6-selenopurine while exhibiting similar or slightly less activity to that of its thiol parent compound proved to be unstable at room temperature, making it a less suitable compound. Attempts to improve the activities of 6-selenopurines by including methyl substituents only served to enhance toxicity [14].

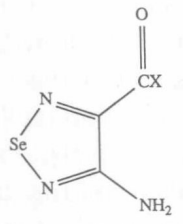
On the other hand, 6-selenoguanine, while exhibiting similar antineoplastic activity in mice to 6-thioguanine, was less toxic than its thiol analogue [13]. Ross et al. [15] studied these two compounds further and compared their activities with those of 6-thioguanosine and 6-selenoguanosine (Table 1). In confirmation of the earlier studies of Mautner et al. [13], mice with sarcoma 180 ascites tumors survived a few days longer on treatment with the selenium compounds than with the thiol compounds, but the improvement was only slight. No company appeared to show interest in this type of compound. Furthermore, the α- and β-2'-deoxy-analogues of 6-selenoguanosine offered no clear advantages over 6-thioguanine [2].

More recently, Maeda et al. [16, 17] have synthesized complexes of 6-mercaptopurine, thioguanine, selenoguanine and selenoguanosine with cis-diaminoplatinum (II). They were unable to identify the structures of the complexes, which they considered to be trans-dimers with molar ratios of platinum to purines of 1:2. In mice with L1210 ascites tumors, the thiol compounds were generally slightly more active in improving survival than the selenium compounds, while the platinum complexes were equally or less active than the parent purines. Despite the lower toxicities of the platinum complexes, their lower activity does not suggest that they offer any marked advantages over the purine parent compounds, particularly since the authors detected slow release in serum of the parent purine from its platinum complex.

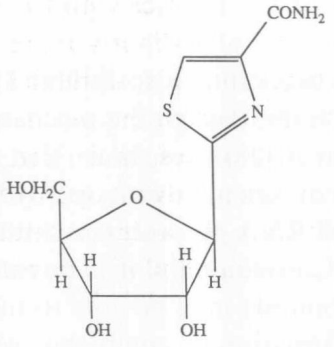
2.2 Selenazoles

In 1967, Shealy and Clayton [18] reported that some 4-amino-1, 2, 5-selenadiazoles (Table 2) were cytotoxic to KB cells in culture. Further studies on these compounds were not reported. Subsequently, the synthesis of 2-β-D-ribofuranosyl-4-thiazole-carboxamide (CI-909; tiazofurin; Table 2) was reported by chemists at ICN Pharmaceuticals [19]. This compound demonstrated weak anti-viral activity, but when given i. p. also produced potent inhibition of L1210 and P388 mouse leukemias and Lewis lung carcinoma *in vivo* [20]. In a synthetic program intended to investigate the structure-activity-relationships of a series of thiazole compounds, it was almost inevitable that the chemists would complement their program with the respective selenazole analogues. The direct analogue of tiazofurin, selenazofurin (CI-935; Table 2) proved to be about 10-fold more cytotoxic than the sulfur an-

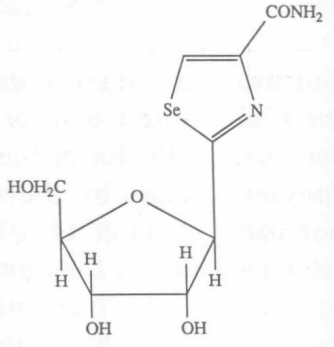
Table 2
Thiazole and selendiazoles with anti-tumor activity



4-amino-1,2,5-selendiazoles



2-ß-D-ribofuranosyl-thiazole-4-carboxamide (CI-909; Tiazofurin)



2-ß-D-ribofuranosyl-selenazole-4-carboxamide (CI-935; PD 111232; Selenazofurin)

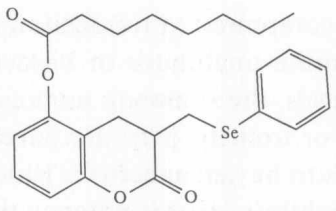
alogue against murine P388 and L1210 cells *in vitro* and was also active against Lewis lung carcinoma *in vivo* [21, 22]. IC_{50} values for selenazofurin in HCT8, WIL2 and L1210 cells lay around 0.3 μmol/l, being 10-fold lower than the respective values for tiazofurin in the former two cell lines and 3-fold lower than for tiazofurin in L1210 cells [23]. Both compounds, injected for 4 days into mice, were markedly active against P388 leukemia, selenazofurin being approximately 8-fold more potent, but at least 4-fold more toxic [23]. In contrast to tiazofurin, selenazofurin was inactive in murine ridgway osteogenic sarcoma *in vivo* at non-toxic doses. Both compounds have a similar mechanism of action as inhibitors of *de novo* purine synthesis. They are metabolized in P388 tumors to ribonucleoside monophosphates and subsequently to analogues of NAD in which the nicotinamide portion of the molecule is replaced by the tiazofurin or selenazofurin [24, 25]. These analogues bind to and inhibit at the NADH binding site of inositol monophosphate (IMP) dehydrogenase, the rate-limiting enzyme in guanylate synthesis, thereby decreasing intracellular guanylate pools and inhibiting RNA and DNA synthesis in P388 cells [19, 22, 23]. Selenazofurin ist approximately 6-fold more potent as an inhibitor of IMP dehydrogenase than tiazofurin [22]. The decrease in guanylate pools also causes guanylate triphosphate (GTP) depletion in HL-60 human leukemia cells *in vitro,* blocking hormone-stimulated increases in cyclic adenosine 3', 5' monophosphate (cyclic AMP) levels and inhibiting chemotactic factor-induced elevation of inositol phosphates [26, 27]. Such actions on intracellular second messengers may contribute towards the anti-proliferative effects of the two drugs.

2.3 Other compounds

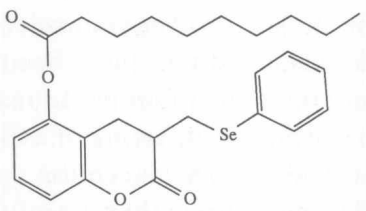
Selenium, as sodium selenite, has been shown to inhibit DNA synthesis in a variety of cells and cell lines, though the mechanism is as yet unclear [10]. Recently, Frenkel et al. [28] have shown that selenotrisulfides, formed by the reaction of selenite with sulfhydryl compounds, are inhibitors of DNA and RNA polymerases, although the selenite itself is a weak inhibitor. Consequently, it is possible that a variety of synthetic selenium compounds may be able to inhibit cell proliferation directly or through formation of complexes with sulfydryl compounds. An example of such a compound is dipentyl-diselenide, which has been patented as a compound with anti-neoplastic activity *in vivo* [29].

Other compounds, like the selenopurines and selenazofurin described above are simply selenium analogues of sulfur-containing compounds with known anti-tumor activities. In addition to several such compounds briefly reviewed by Shamberger [2], but apparently not pursued, several new compounds have been reported recently. The structures of these compounds are given in Table 3. 5-Hydroxy-3-[(phenylseleno) methyl] hydrocoumarinoctanoate (3d) and the respective decanoate were found to be inhibitors of human colon 8r cell proliferation, probably through formation of the corresponding α-methylene lactones [30]. Benzylseleno-cyanate, the analogue of benzylthiocyanate, administered in the diet, inhibited intestinal carcinogenesis induced by azoxymethane in rats and benzo(a)pyrene-in-

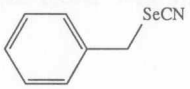
Table 3
Miscellaneous organoselenium compounds with anti-tumor activities



5-hydroxy-3-[(phenylseleno)methyl] hydrocoumarin octanoate

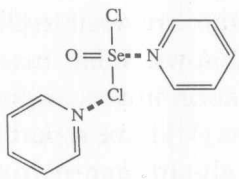


5-hydroxy-3-[(phenylseleno)methyl] hydrocoumarin decanoate



benzylselenocyanate

p-methoxybenzeneselenol



selenium oxychloride-pyridine complex (1:2)

duced forestomach tumors in mice [31, 32]. Benzylthiocyanate was inactive in both tests at the same dose (25 ppm in rats, 0.045 μmol/g diet in mice, given prophylactically). Similarly p-methoxybenzeneselenol was an effective chemopreventive agent in mouse forestomach tumorigenesis (at 3.3 μmol/g diet) and azoxymethane-induced hepatocarcinogenesis in rats (at 50 ppm in the diet), though p-methoxyphenol was also highly effective in the mouse model [32,33]. A compound described recently by scientists at Nippon Kayaku is selenium oxychloride-pyridine complex [34]. This compound is antiproliferative against Hela 53 cells *in vitro* ($IC_{50} = 0.59\ \mu g/ml$) and inhibits Ehrlich ascites carcinoma in mice when given i. p. at 2 mg/kg. However, the therapeutic index is low, so that it seems unlikely that the compound will be developed further.

2.4 Conclusions

The majority of organo-selenium compounds investigated for antineoplastic activity have been selenium analogues of known sulfur-containing compounds. In many cases, the selenium analogues offer no advantage in terms of efficacy or toxicity over the parent sulfur compounds. The exception appears to be selenazofurin which, while being more toxic than tiazofurin, exhibits greater potency and probably a greater therapeutic index. Clinical data have yet to be published.

3 Compounds for reduction of side effects of anti-cancer antibiotic therapy

Daunorubicin (Cerubidine®) and doxorubicin (Adriamycin®) are antibiotics widely used for cancer chemotherapy, the former for acute leukemias, the latter for solid tumors. The clinical usefulness of both drugs is however limited by a selective cardiotoxicity which is related to the total dose of the drug and is often irreversible [35]. While the mechanism of this cardiotoxicity is unknown, it has been shown that both compounds induce lipid peroxidation in the cardiac tissue [36]. Furthermore, Doroshow and colleagues [37] have reported that doxorubicin depletes selenium-dependent glutathione peroxidase in the heart and its cardiotoxicity is enhanced by feeding mice a selenium-deficient diet. More recently Dimitrov and colleagues [38] have re-