Developments in the chemistry of selenaheterocyclic compounds of practical importance in synthesis and medicinal biology

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Dedicated to Prof. Jan Epsztajn on the occasion of his 75th birthday

Abstract
The heterocyclic compounds with selenium atom in the ring such as selenirenes, selenophenes, selenadiazoles, selenatriazoles, benzisoselenazolones and some others are presented as the reagents and intermediates employed in synthesis of alkenes, alkynes and nonseleminium heterocycles or as the catalysts for hydroperoxide oxidation of various groups of organic compounds. Selenaheterocyclic compounds, particularly the benzisoselenazol-3(2H)-ones and other cyclic selenenamides, selenenate esters, spirodioxyselenuranes, selenium-containing nucleoside analogues, selenazines and selenazoles are shown as antioxidants, anti-inflammatory agents, virucides, bacteriocides, fungicides, cytokine inducers and immunomodulators. The chemical and biological activity of the presented compounds and the mechanisms of their action are discussed.

Keywords: Anti-infective agents, antioxidants, deselenation, oxidation, selenium compounds

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1. Introduction

The first report on synthesis of an organoselenium compound, diethyl selenide, was in 1836.\textsuperscript{1} It was until 1970s, when the discovery of several useful new reactions and a variety of novel structures with unusual properties began to attract more general interest. The interest in the use of organoselenium compounds, among them these having different selenium-containing heterocyclic systems, as potential pharmaceuticals, new materials as well as reagents and catalysts expanded rapidly during last three decades and lot of works concerned in this field have been published.

This review covers the scientific literature from 1990 to the present, but includes several significant earlier references where necessary for discussion. A number of reviews on selenaheterocyclic compounds, or more generally on organoselenium compounds including selenaheterocycles, has been published during last ten years.\textsuperscript{2} They gave a broad overview of the reactions, syntheses and structural determination. There were also reports and some reviews on the prospective practical applications of organoselenium compounds as reagents and catalysts\textsuperscript{3}, pharmaceuticals\textsuperscript{4} and electroconducing materials\textsuperscript{5}, where selenaheterocycles were mentioned.

A large number of original papers concerned with the chemistry, and biology of selenaheterocyclic compounds have been published recently. Since referring of all of them would be beyond the scope of this article we refer these of them which in our opinion emphasize modern trends in practical organic chemistry related to new methodologies for organic synthesis and to medicinal chemistry. Several of these works have been done in our laboratory, and we present them in this article referring briefly some newest unpublished results. We would like to apologize to anyone who finds our description of her or his work inadequate or whose work we have omitted.

2. General aspects of the selenaheterocyclic compounds chemistry

The structures of selenaheterocyclic compounds are closely related to those of analogous sulfur compounds, but their properties often present marked difference. In these compounds the selenium atom is mainly bivalent although no information is available about the nature of the selenium orbitals in the bivalent state of selenium. The representatives are common cyclic selenides (eg. 1), diselenides (eg. 2) or even polyselenides (such as hexaselenacyclooctane 3)\textsuperscript{6}, selenosulfides, and others. In tetravalent selenium compounds such as cyclic selenoxides 4,
selenonium salts (eg. 5)\textsuperscript{7a} and selenuranes 6 a tetragonal structure arises from sp\textsuperscript{3} hybridization of the selenium atom. When three different substituents are bonded to the Se (4, R≠H) the selenium atom is a stereogenic center. In selenuranes the structure is a trigonal bipyramide and two most electronegative substituents are located in apical positions (6, X = halogen, OH, OR). The electron pair or the unfilled orbital of the selenium atom, can be conjugated with carbon or heteroatom (mainly nitrogen) \(\pi\)-electron ring system such as for example well known selenophene 7 or less common selenopyrylium salts (eg. 8)\textsuperscript{7b}. Hexacoordinated selenium does appear in organic chemistry uniquely. The examples, selenurane oxide 9\textsuperscript{8} and selenophene dioxide 10\textsuperscript{9} are given in Figure 1.

![Chemical structures](image)

**Figure 1**

In the most selenaheterocyclic rings the selenium atom is bounded to carbon or to the heteroatom, such as Se (eg. 2, 3), O (eg. 9), N (eg. isoselenazole 11) or S (eg. selenosulfide 12).\textsuperscript{10} Some of selenaheterocyclic systems containing Se-Te, Se-P, Se-B, Se-Zn or Se-Sn bonds which examples 13-17 presented in Figure 2, were also reported.\textsuperscript{11}
Above two hundred different selenium-containing saturated, unsaturated and aromatic ring systems are known. Majority of these compounds have the five and six-membered rings and generally they are thermodynamically stable. Thermodynamical stability and chemical properties of cyclic selenides and diselenides are similar to their open chain analogues. For example, the properties of tetrahydrofuranselenophene 1 are similar to these of dialkyl selenides. In some cases, when selenium is bounded to a more electronegative atom, such as in the cyclic derivatives of selenenic acid (R-SeOH) - selenenoesters, anhydrides or selenenamides 18, their stability is substantially higher than products of ammonolysis 20 which spontaneously convert to diselenides 21, as it is shown in Scheme 1. These compounds are additionally stabilized by condensed aromatic or heteroaromatic rings. For example, contrary to stable benzisoselenazol-3(2H)-ones 18, isoselenazol-3(2H)-ones 19 (Scheme 1) remain unknown. Some of five-membered heterocycles such as 1,2,3-selenadiazoles and selenatriazoles easily extrude, in the thermal conditions, selenium and nitrogen.
Scheme 1

Three-membered ring selenaheterocycles – seleniranes are substantially less stable than thiiranes or oxiranes. They easily decompose to alkenes and elemental selenium. The seleniranes, and their unsaturated analogues selenirenes, have been postulated as active intermediates.\textsuperscript{2a} To our knowledge the stable selenirane 22 is an exception.\textsuperscript{8b,13} There exist only a few examples of selenetanes and diselenetanes obtained as stable compounds.\textsuperscript{14} 2-phenylselenetane 23 is an example (Figure 3).\textsuperscript{14a}

A number of the macrocyclic compounds containing one or more selenium atoms, and also other heteroatoms such as N, P, O and S are known. The rings vary from seven-membered to eighteen-membered. Most of the works on such compounds has been directed towards their synthesis, with some emphasis on their conformations, reactions and heavy metal complexation.\textsuperscript{4f,15} The examples are compound 24\textsuperscript{15a} and selenaporphyrin 25.\textsuperscript{15b} Unlike the smaller rings, aromatic examples are absent.

It should be mentioned that it is commonly thought that organoselenium compounds are malodorous and toxic. The low volatile selenaheterocyclic compounds are odourless and their toxicity should be low. For example, mentioned in Chapter 3, 2-phenylbenzisoselenazol-3(2\textsubscript{H})-one (ebselen) is practically nontoxic (LD\textsubscript{50}=6.8 g/kg).\textsuperscript{4d} From twenty years in our laboratory practice we worked with different these compounds without any special precautions although we carefully avoided of their direct contact with the skin, eyes and mouth.
3. Selenaheterocyclic compounds of practical importance

3.1. Reagents, catalysts and intermediates in synthesis of non-selenium compounds
During last thirty years the long-standing but modest use of selenium reagents by organic synthetic chemists received a new impetus. Among numerous organoselenium reagents, catalysts and intermediates employed in synthesis of selenium-free compounds only a few of them were selenaheterocyclic. Nevertheless, their role, in some synthetically useful reactions is prominent and worthy of note. The reactions can be divided on two groups: these which proceed through extrusion of the selenium in the thermal or reductive conditions, or under treatment with a nucleophile (photochemical extrusion of the selenium is of minor importance for use in synthesis) and these where selenium plays a role of the oxygen-transfer agent.

3.1.1. Reactions involving deselenation
Although only a few examples of relatively stable three-membered heterocycles containing selenium atom are known their thermolability has been utilized successfully in several synthetic reactions such as stereospecific transformations of epoxides to alkenes, synthesis of strained cycloalkynes, sterically congested alkenes, and azomethines. All these reactions proceeds via extrusion of selenium. The example is decomposition of the stable selenirane by the treatment with hexamethylphosphorus triamide in chloroform at room temperature resulted in formation of deselenated alkene.

Figure 3
Deselenation of intermediate seleniranes has been postulated as a step of two other important reactions: isomerization of alkenes (Scheme 2) and stereoselective deoxygenation of oxiranes (Scheme 3).

The treatment of bromohydrin 27, easily prepared from alkene 26, with selenocyanate anion leads to the β-hydroxyselenocyanate 28, which in the basic medium gives the selenirane 29 and finally alkene 30 with reverse configuration.\(^\text{16}\)

![Scheme 2](image)

Scheme 2

When oxiranes 31 are treated with selenocyanate anion the reaction proceeds via intermediates 32 and 33 to selenirane 34. Extrusion of selenium from 34 results in alkenes 35.\(^\text{17}\)

Unstable seleniranes are the intermediates when other reagents such as triphenyl- and trialkylphosphine selenides, trialkylammonium \(O,O\)-dialkyl phosphoroselenoates, \(N\)-methylselenoxobenzothiazoles and selenoamides are used in the stereospecific deoxygenation of oxiranes to alkenes.\(^\text{2a,3a,18}\)

![Scheme 3](image)

Scheme 3
Seleniranium cation 37 is formed by the addition of organoselenium electrophile 36, generated in situ by treatment of the corresponding diselenide with Br₂ and AgOTf, to alkene. The intermediate 37 is then attacked by a nucleophile from the anti-side leading to addition products of type 38 (Scheme 4). Selenides 38 can undergo various subsequent reactions and are therefore versatile building blocks in stereocontrolled organic synthesis. A number of selenium chiral electrophiles have been employed in these reactions.¹⁹

Scheme 4

Two-fold extrusion of the nitrogen and selenium from selenatriazoles and selenadiazoles is a good method for synthesis of different compounds. Unstable selenatriazoles 40, formed in situ from selone 39 and phenyl azide, decompose to selenaaziridines 41 and gives ketimines 42 as the final products.²⁰ The sterically crowded olefines 45 can be obtained from selenadiazolines 43, produced from 39 and diazo compound, decomposed via selenirane 44. In this manner, from selenadiazoline 46 some extremely hindered olefines, among them 47 (Scheme 5), were obtained.²¹

Scheme 5
The ready thermal and photochemical decomposition of 1,2,3-selenadiazoles 50 resulting in extrusion of nitrogen and selenium or nitrogen only has been exploited widely in synthesis from more than thirty years.\textsuperscript{3a} They are easy to obtain from semicarbazones 49, derived from ketones 48, and selenium(IV) oxide in acetic acid. The thermolysis of 50 or its decomposition with butyllithium gave the alkyne (Scheme 6).\textsuperscript{22} More recently some new reactions, among them thermolysis of 1,2,3-selenadiazoles fused to carbocyclic rings to cycloalkynes, were elaborated.\textsuperscript{23}

![Scheme 6](image)

Scheme 6

The valuable synthetic intermediates are 2,1,3-benzoselenadiazoles. They were used for preparation of \(N\)-alkyl-1,2-benzenediamines, 3-nitro-1,2-benzenediamines, 3,4-diamino-2-nitrophenols and 5-nitroquinoxalines.\textsuperscript{24} The key step of the reaction is their reductive deselenation. The example is shown in Scheme 7. 4-Methoxy-1,2-benzenediamine 51 and selenium(IV) oxide give 2,1,3-benzoselenadiazole 52 subsequently nitrated to the nitro derivative 53. The reductive deselenation of 53 by ammonium hydrosulfide yields the product 54. Treatment of 53 with hydroiodic acid removes both selenium and methoxy group and 1,2-diamino-3-nitrobenzene 55 is produced but this reaction has not a synthetic value due to large amount of HI used.\textsuperscript{25}
Scheme 7

[1,4]-Cycloaddition of the active dienophiles to 2,1,3-selenadiazoles accompanied by deselenation is a convenient way for construction of non-selenium azaaromatic rings. The conversion of 2,1,3-selenadiazole 56 into pyrazine 57 (Scheme 8), is an example.\textsuperscript{26}

Scheme 8

Even thermodynamically stable aromatic selenaheterocycles such as selenophene 7 undergo [1,4]-cycloaddition followed by deselenation. On heating of selenophene with maleic anhydride selenium is extruded and diene 58 is formed (Scheme 9).\textsuperscript{27} The NiCl\textsubscript{2} catalyzed reaction of Grignard reagents induces the ring opening of selenophenes, with loss of the chalcogen atom, giving the \textit{s-cis}-1,3-butadiene.\textsuperscript{28}

Scheme 9
The salt 59, readily obtained from dibenzoselenophene, is a powerful methylation agent even in water as a solvent while 60 can be used as a trifluoromethylating electrophile (Scheme 10) although the sulfur analogues are more reactive.29,30

![Scheme 10](image)

Nucleophilic reaction of cyclic chloroselenurane 61 with lithium \(N\)-protected amides afforded chiral allylic selenimides 62 as intermediates with retention of configuration. A sigmatropic [2,3]-rearrangement of 62 yielded chiral \(N\)-protected allylic amides 63 up to 93 % ee.31

![Scheme 11](image)

3.1.2 Oxygen-transfer reactions
Selenium(IV) oxide and nonheterocyclic organoselenium compounds, such as selenoxides, benzeneseleninic acid, its anhydride and analogues were employed, at the last three decades of
the past century, as the stoichiometric reagents for oxidation of different groups of organic compounds. Now, they fall into desuetude because they are not fulfill the requirements of modern organic synthesis. They were used in relatively bulky amounts, were expensive and, beside of a few exceptions, could not be regenerated. The exception is a still employed selenium(IV) oxide.\(^{3h}\)

Two selenaheterocyclic compounds, chloroselenurane 64 and chiral selenoxide 65 (Figure 4) were reported recently as highly chemoselective reagents for oxidation of sulfides to sulfoxides although stereoselectivity, expected for 65, was low.\(^{32}\)

![Figure 4](image)

More attractive approach has been based on the using of organoselenium compounds as the catalysts when the stoichiometric oxidant is 30% aqueous hydrogen peroxide or 80% tert-butyl hydroperoxide (TBHP). For the many reactions diaryl diselenides, and benzisoselenazol-3(2\(H\))-ones 18 (particularly ebselen, 18, R = Ph), used in 5% molar amount, (related to the substrate), were the most effective catalysts.\(^{3h,3i}\) Ebselen has been known as mimetic of enzyme glutathione peroxidase, able to interact with active oxygen species present in the living cells (see Chapter 3.2) but its using in nonenzymic conditions as catalyst for hydrogen peroxide oxidation of thiols such as \(N\)-acetylcysteine, butanethiol and octanethiol to disulfides gave poor results.\(^{33}\) Nevertheless, the selenenamide derived from camphor effectively catalyzed oxidation of phenylmethanethiol to the disulfide.\(^{34}\)

We provided the evidence that ebselen is one of the most versatile oxygen-transfer catalyst among organoselenium compounds. There have been several reactions (presented in Scheme 12) elaborated in our laboratory where stoichiometric oxidants are hydrogen peroxide or TBHP and ebselen is a catalyst. There are: selective oxidation of sulfides to sulfoxides 66\(^{35}\), oxidation of the oximes, in the presence of primary or secondary alcohols to esters 67\(^{36}\), oxidative conversion of \(N, N\)-dimethylhydrazones or benzylamines into nitriles 68\(^{37,38}\), regeneration of the parent ketones 69 from azines\(^{36}\), dehydrogenation of tetrahydroisoquinoline to isoquinoline 70\(^{38}\), epoxidation of cyclooctene to epoxide 71\(^{39}\) and oxidation of aromatic aldehydes to arenecarboxylic acids 72 with avoiding of the Baeyer-Villiger rearrangement.\(^{40}\) All these reactions have practical value since procedures are simple and the products can be isolated in high to excellent yields. The reaction conditions and the results suggest the ionic mechanism.

Despite of the reactions of ionic mechanism, other reactions, presented in Scheme 13, show that free-radical mechanism can also take place. Catalyzed by ebselen TBHP oxidation of
alkylarenes to alkylaryl ketones 73,36 anthracene to antraquinone 74, 2-methyl-1,4-dimethoxynaphthalene to 2-methyl-1,4-naphthoquinone 7531 and oxidative coupling of 2-aminophenol to phenoazinone 7642 gave results similar to these when one-electron oxidants such as, cerium(IV), silver(II) or Mn(III) were the reagents. Moreover, oxidation of azine derived from 2-acetylp yridine gave the mixture of expected ketone 77 and condensed triazole 78.36 The same result was found when cerium ammonium nitrate was used as the reagent. It suggests that the reaction proceeds via cation-radicals.

**Scheme 12**

- **R³SR², H₂O₂, MeOH**
  - 20°C, 3-48 h
  - **66** 92-95%

- **ArCH=N-OH, H₂O₂, MeOH**
  - **ArCOOMe**
  - 20°C, 62-180 h
  - **67** 62-82%

- **ArCH=NNMe₂, H₂O₂, MeOH**
  - **R-CN**
  - 20°C, 62-180 h
  - **92-98%**

- **ArCH₂NH₂, TBHP, tert-BuOH, reflux, 20 h**
  - **R³-CO-R⁴**
  - 62-90%

- **H₂O₂ or TBHP t-BuOH, reflux, 20 h**
  - **70** 58%
  - **71** 60%

- **ArCHO, TBHP, t-BuOH**
  - 75°C, 24-120 h
  - **ArCOOH**
  - **72** 58-99%
Scheme 13
The evidence has been made that the active intermediate formed from ebselen (18, R=Ph) by treatment with hydroperoxide is hydroperoxyselenurane 79.\textsuperscript{40} It have the hydroperoxy group the same as is present in areneperoxyselenenic acids ArSe(O)OOH formed \textit{in situ} by hydroperoxide oxidation of diaryl diselenides.\textsuperscript{43} The hydroperoxyselenurane 79 can form two active species – the anion 80 or radical 81 (Scheme 14).

\begin{center}
\includegraphics[width=\textwidth]{scheme14.png}
\end{center}

**Scheme 14**

The role of ebselen in the reactions of ionic mechanism such as for example chemoselective oxidation of aromatic aldehydes to arene carboxylic acids with TBHP can be explained as shown in Scheme 15.\textsuperscript{40} Consistent with the widely accepted mechanism for reaction of carbonyl compounds with peroxy acids, the first step is addition of 79 to the carbonyl compound 82 to form a tetrahedral intermediate 83. The next step of the Bayer-Villiger rearrangement, which is rate determining, should be migration of the aryl group to the electrophilic oxygen atom of the peroxide bridge and simultaneously, cleavage of the O-O bond along with release of hydroxyselenurane R\textsuperscript{1}OH. The phenol 84 should be the final product. Nevertheless, two bulky groups R\textsuperscript{1} and R\textsuperscript{2} in the vicinity of the electrophilic oxygen atom in the peroxide bridge hinder aryl migration and competitive hydride ion migration predominates. This pathway leads to ester 85 and finally to the acid 86.
The oxidation of active methylene group in alkylarenes to carbonyl group is an example where hydroperoxyselenurane 79 is involved in a postulated free-radical mechanism shown in Scheme 16. In the first step of the reaction one-electron transfer, from the substrate 87 to the oxidant 81 take place and the cation 88 and anion 95 are formed. The deprotonation of 88 by 95 leads to the benzyl radical 89, oxidized to the benzyl cation 90 which treating with water gives benzyl alcohol 91. In the next steps of the oxidation and deprotonation the intermediates 91-94 are formed and finally ketone 73 is produced. The same result is obtained when the alcohol 91 is a starting substrate. Protonation of 95 leads to hydroxyselenurane 96, which is subsequently oxidized to hydroperoxyselenurane 79 by TBHP and the active radical 81 is regenerated.
In our previous works we reported that other 2-substituted benzisoselenazol-3(2H)-ones and their open-chain analogues 2-(carbamoyl)phenyl diselenides also exhibited appreciable catalytic activity. Also 1,3,2-benzothiaselenazole 1,1-dioxides were found as the effective catalysts for
the hydroperoxide oxidation of cycloalkanones to cycloalkanecarboxylic acids and 2-methyl-1,4-dimethoxynaphthalene to 2-methyl-1,4-naphthoquinone.\textsuperscript{45} We expected that new chiral benzisoselenazol-3(2\textsubscript{H})-ones \textbf{97-100} (Figure 5) should be catalysts for stereoselective hydroperoxide oxidation of prochiral sulfides. Unfortunately, none of stereochemical effects were observed and only racemic sulfoxides were produced in high yields.\textsuperscript{46}

![Chemical structures](image)

**Figure 5**

Covalent immobilization of homogenous catalysts to insoluble solid supports has received considerable attention in modern organic synthesis and a number of them has been reported recently.\textsuperscript{47} We undertook the effort to immobilize the benzisoselenazolones to silica or polymer support. The silica-supported catalyst \textbf{101} was obtained in the reaction of 3-aminopropytriethoxysilane with 2-(chloroseleno)benzoyl chloride and subsequent hydrolysis of formed by-product. The preliminary study confirmed its activity, similar to the activity of ebselen, in hydrogen peroxide oxidation of sulfides to sulfoxides and/or sulfones, and in TBHP oxidation of alkylarenes to alkylaryl ketones. The catalyst can be easily filtered off from the mixture after the reaction and reused.\textsuperscript{48} 4-Aminostyrene treated with 2-(chloroseleno)benzoyl chloride in the presence AIBN gave ebselen covalently immobilized on a polyethylene chain \textbf{102}. Other polymer-supported benzisoselenazol-3(2\textsubscript{H})-ones were \textbf{103} and \textbf{104}. The catalyst \textbf{103} was obtained by acylation-selenenylation of primary amino groups in 1-aminohexylamine gel with 2-(chloroseleno)benzoyl chloride, while the catalyst \textbf{104} was the aminoebselen supported on the Merrifield resin.\textsuperscript{31,49} The studies on the catalytical properties of polymer-supported benzisoselenazol-3(2\textsubscript{H})-ones are in progress.
There are three different methods for synthesis of ebselen and other benzisoselenazol-3(2H)-ones. One of them involves ortho-lithiation of benzanilide, selenium insertion, and oxidative cyclization.\textsuperscript{50} A free-radical synthesis of ebselen has been achieved by \textit{t}-butyl or benzoyl peroxide-mediated cyclization of 2,2’-diselenobis(benzamides).\textsuperscript{51} Third, the most versatile approach was elaborated in our laboratory as a modification of the classical procedure reported by Lesser and Weiss (Scheme17).\textsuperscript{52} The first two steps of the synthesis involve diazotization of anthranilic acid \textit{105} and selenenylation of diazonium salt with disodium or dilithium diselenide, generated \textit{in situ} from elemental selenium and sodium or lithium and hydrazine hydrate in the alkaline medium. The formed acid \textit{106} treated with excess of thionyl chloride in the presence of catalytical amounts of DMF, gives 2-(chloroseleno)benzoyl chloride \textit{107} which is a reagent for tandem selenenylation-acylation of primary amino groups giving a variety of 2-substituted benzisoselenazol-3(2H)-ones \textit{18}, among them ebselen.\textsuperscript{52b-d}

Scheme 17
3.2. Bioactive compounds

The biochemistry and pharmacology of selenium compounds, among them selenaheterocycles are subjects of intense current interest, especially from the point of view of public health. During last few years, a tremendous effort has been directed toward the synthesis of stable organoselenium compounds that could be used as antioxidants, enzyme modulators, antitumors, antivirals, antimicrobials, antihypertensive agents and cytokine inducers. Their possible applications as therapeutic agents in treatment of several diseases has been revealed in numerous papers and recently discussed in the reviews.4d-f

3.2.1. Antioxidants and anti-inflammatory agents

Reactive oxygen species such as hydroxyl radical, superoxide anion and peroxynitrite are involved in many cellular processes including the inflammatory response. The best known anti-inflammatory compound is ebselen. It has undergone Phase III clinical trials as a neuroprotective agent and is soon to become the first synthetic organoselenium therapeutic released on the market.

Ebselen acts as glutathione peroxidase (GPx) mimic by reducing hydroperoxides to water or the corresponding alcohol. The postulated mechanism of the enzyme-like action of ebselen is presented in Scheme 18. When concentration of hydroperoxide is high ebselen is oxidized to selenoxide 108 which reacting with one molecule of the thiol gives selenosulfide 109. The intermediate 109 and the second molecule of thiol produce disulfide while the formed selenenic acid 110 is converted back to the ebselen. In the biological systems, where concentration of hydroperoxide is low, ebselen and thiol give the selenosulfide 111 which disproportionates to the disulfide and diselenide 112 which is subsequently oxidized to selenenic anhydride 113 and finally to ebselen.4a,4c

More recently it has been demonstrated that ebselen is also able to catalytically reduce hydroperoxides through reaction with the thioreductase (Trx) system.4f,53 Inflammatory enzymes known as the lipoxygenases (LOX) and cyclooxygenases (COX), activated by hydroperoxides, are attractive targets for inhibition in the pursuit of anti-inflammatories such as ebselen and others. The capacity for ebselen to act as LOX inhibitor is critical to its anti-inflammatory activity. The inhibition of LOX by ebselen may be as a result of its anti-oxidant activity or through the direct its interaction with the enzyme.4f
The activity of ebselen can be altered by modifying its structure. Substitution of hydrogen atom with a nitro group in the ortho-position to selenium (114, Figure 7) has been shown to increase the GPx activity of ebselen.\textsuperscript{54} It is noteworthy that the sulfur analogue of ebselen is inactive. The compounds such as 115 and 116, having no Se-N bond, are also inactive or their activity is only 0.033 times as active as ebselen.\textsuperscript{4c,4f,55} Several research groups have prepared different compounds having selenenamide moiety in the heterocyclic ring.\textsuperscript{4c,4d} The camphor-derived cyclic selenenamide 117 and selenenamides 118, 119 having supplementary tetrahedral
carbon in the ring display appreciable GPx mimetic activity. The compound 119 showed higher GPx-activity than ebselen and potent inhibition of TNF-α induced endothelial alterations. It has been actually in clinical development as drug candidate for the treatment of ulcerative colitis.56 Other representative selenaheterocyclic compounds containing Se-N bond 120, 121 mimic the biological activity of GPx are shown in Figure 7.57

Selenaheterocyclic compounds having Se-O instead of Se-N bond were synthesized and evaluated as GPx mimetics. There were cyclic seleninate esters 122, 123 and spirodioxyxelenuranes 124, 125 tested for catalytic activity in a model system wherein TBHP or hydrogen peroxide was reduced with the benzyl thiol. The most efficient catalysts were 122 and 124, substantially more active than ebselen.58

The efficacy of ebselen is somewhat limited by its low water solubility. In the pursuit of preparing GPx mimics β-cyclodextrins with ebselen moiety tethered to the primary ring were obtained. These compounds had excellent solubility and cyclodextrin 126 displayed GPx activity on par with that of ebselen.59

3.2.2. Enzyme inhibitors
Organoselenium compounds are known to inhibit a variety of enzymes such as nitric oxide synthase (NOS), inosine monophosphate dehydrogenase (IMDPH), lipoxygenases (LOX), uridine phosphorylase (UrdPase), thymidylate synthase (TMS), tyrosine kinase (TK), NADPH oxidase, protein kinase C (PKC), glutathione-S-transferase (GST), NADPH-cytochrome reductase and papain.4d Several selenaheterocyclic compounds active against NOS, IMPDH and LOX may be considered as potential pharmaceuticals.

Ebselen and related organoselenium compounds, among them carboxylated analog 127, have been reported to be inhibitors of constitutive endothelial NOS (ecNOS).60 Further, as an extension of these studies some other benzisoselenazol-3(2H)-ones 128-135 (Figure 8) have also been synthesized and evaluated for their inhibitory properties in rabbic aortic rings.52b The observed difference in the activity of two enantiomers 134 and 135 may be due to the stereospecific interactions between the inhibitor and the enzyme. Selenourea derivatives, among them 2-aminoselenazoline 136 have also been reported as potent inhibitors of the iNOS.61
Figure 7

Figure 8
Since the activity of IMPDH increases significantly in proliferating cells, the IMPDH inhibitors are expected to be promising antitumor and immunosuppressive agents and have been considered as potentiators of the anti-HIV activity of retroviral drugs such as 2’,3’-dideoxyinosine. Selenazofurin 137, selenophenfurin 138 and dinucleosides, such as for example 139 (Figure 9), are potent IMPDH inhibitors and have pronounced antitumor activity in animals, and broad spectrum antiviral as well as maturation-inducing activities. The inhibitory effects of heterocyclic organoselenium compounds such as ebselen and some of its derivatives 140-142 have been demonstrated on 15-LOXs.

![Chemical structures](image)

**Figure 9**

### 3.2.3. Antitumor agents

Despite very promising research, to date, no synthetic organoselenium compounds are in clinical use as anti-cancer agents. The applicability of selenaheterocyclic compounds in tumor control has been demonstrated in five-membered ring system. The search for novel antitumor agents resulted in the successful development of the two prospective compounds 143 and 144 (Figure 10) that were tested against tumor growth in a mouse model. Both of them markedly inhibited the growth of P388 mouse leukemia at dose 100 µg/mouse/day without exhibiting any toxicity. 2,4-Disubstituted selenazoles 145 and 146, evaluated for their antitumor activity by determining their ability to inhibit proliferation of L1210 cells *in vitro*, exhibited appreciable activity, although the selenazole 146 was less potent compared with sulfur analog.
A number 1,3-selenazine and selenazole derivatives have been reported antiproliferative agents. The most active against human fibrosarcoma HT-1080 cells were selenazines 147 and 148. Further, certain 2-phosphonoalkylbenzisoselenazol-3(2H)-ones 149 were synthesized and their potent activity against human carcinoma cells in vitro was reported.

\[
\begin{align*}
143 & \quad N\begin{array}{c}
\text{O} \\
\text{Ph}
\end{array}N\begin{array}{c}
\text{N} \\
\text{Se}
\end{array} \\
144 & \quad N\begin{array}{c}
\text{Me} \\
\text{Ph}
\end{array}N\begin{array}{c}
\text{N} \\
\text{Se}
\end{array} \\
145 & \quad \text{R} = \text{CH}_2\text{Cl} \\
146 & \quad \text{R} = \text{SCN} \\
147 & \quad \text{R} = \text{Et} \\
148 & \quad \text{R} = \text{n-Pr}
\end{align*}
\]

Figure 10

3.2.4. Anti-infective agents
Selenium containing antivirals, usually in the form of nucleoside synthetase inhibitors, are selenazofurin (mentioned in the Chapter 3.2.2) and oxaselenolane nucleoside 150. While bearing a broad spectrum of antiviral activity, unfortunately selenazofurin 137 is highly toxic at therapeutic concentrations making it an unsuitable therapeutic. Compounds such as 150 show in vitro activity against HIV at nanomolecular concentrations, below the level at which toxicity is observed.

The 7-azabenzisoselenazol-3(2H)-ones 151 substituted at 2-position with phenyl or alkyl groups and the methiodides 152, were found in the antiviral assay to be strong inhibitors of cytopathic activity of herpes simplex type 1 virus (HSV-1) and encephalomyocarditis virus (EMCV), more potent than ebselen. The minimal inhibitory concentration (MIC) values were in a range 0.4-6.0 µg/ml substantially lower than these when toxicity was observed. The vesicular stomatis virus (VSV) remained resistant toward tested compounds, except moderately active methiodide 153.

The antibacterial activities of ebselen and several other benzisoselenazo-3(2H)-ones against Gram-positive and Gram-negative bacteria have been reported and it has been postulated that their action is due to the reactivity with essential thiol groups. Ebselen as well as the p-
chloro analogue 154 exhibited strong inhibitory activity against the growth of fungi *Saccharomyces cerevisiae* and *Candida albicans* strains. Several benzisoselenazo-3(2H)-ones were tested *in vitro* against pathogenic bacteria, yeasts and filamentous fungi *Aspergillus niger*, *Penicillum chrysogenum* and *Penicillum citrinum*. The broadest spectrum of activity was observed for the 2-methyl-7-azabenzisoselenazol-3(2H)-one (151, R= Me) (MIC=2.0-32.0 µg/ml).

![Chemical structures](image)

**Figure 11**

### 3.2.5. Cytokine inducers and immunomodulators

The cytokines such as interleukines (ILs), interferons (IFNs) and tumor necrosis factors (TNFs) are the stimulants which play an important role in the mammalian immunological systems. It was revealed that ebselen, several other benzisoselenazo-3(2H)-ones and open-chain bis(2-carbamoyl)phenyl diselenides induce cytokines IL-2, IL-6, TNF-α and IFN-γ in the human blood leucocytes. Among the benzisoselenazol-3(2H)-ones the highest activity exhibited ebselen and the compounds 155, 156 (Figure 12). Several benzisoselenazol-3(2H)-ones were also studied for their immunological activities in mouse, rat cells and chickens. These studies suggest that the process of cytokine inducing by organoselenium compounds is species-specific. The drugs which were active in the human PBL were found to be inactive in the mouse, rat and bovine cells.
Figure 12

4. Conclusions

In conclusion we wish to say that selenaheterocyclic compounds particularly selenirenens, selenophenes, selenadiazoles, selenatriazoles are key intermediates employed in synthesis of alkenes, alkynes and selenium-free heterocycles. Others, such as benzisoselenazol-3(2H)-ones are the efficient oxygen-transfer catalysts for hydroperoxide oxidation of various groups of organic compounds and most of these reactions have a synthetic value because of their selectivity and high yields of the products. The unique redox properties of selenium are influential in the catalytic and biological activities of organoselenium compounds, among them these where selenium is a part of the heterocyclic ring. Selenaheterocyclic compounds, particularly the benzisoselenazol-3(2H)-ones and other cyclic selenenamides, seleninate esters, spirodioxyselenuranes, selenium-containing nucleoside analogues, selenazines and selenazoles possess therapeutic potential against various diseases as antioxidants, enzyme inhibitors, anti-inflammatory and anti-infective agents, and immunomodulators. We hope that the progress and perspectives emphasized in this review will direct the attention, not only organoselenium community, but also other organic chemists, biochemists and medicinal biologists on the selenium-containing heterocyclic compounds.

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References


