Biologically significant selenium-containing heterocycles

Masayuki Ninomiya,[a] Dinesh R. Garud[b] and Mamoru Koketsu[a,*]

Department of Materials Science and Technology, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

Department of Chemistry, Sir Parashurambhau College, Tilak Road, Pune 411 030, India

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Contents

ABSTRACT

Selenium represents an essential element for organisms as various diseases can result from selenium deficiency. As a consequence, selenium-containing heterocycles are of considerable biochemical and pharmacological relevance. Selenium-containing heterocycles are often less stable than the corresponding sulfur analogues. Therefore, the investigation of new methods for the synthesis of small selenium-containing building blocks is of considerable interest. This review describes the use of biologically significant selenium-containing heterocycles from the viewpoint of chemical structures.

1. Introduction

The element Selenium was first discovered in 1817 by the Swedish chemist Berzelius, [1] and was named after the Greek goddess of the moon, Selene. He observed the element as a deposit following oxidation of sulfur dioxide from copper pyrites. Selenium has an atomic number 34, an atomic weight of 78.96, and is located between sulfur and tellurium in Group 16 in the Periodic Table. It is distributed in the Earth's crust at concentrations averaging 0.09 mg/kg. Its six major stable isotopes have been

* Corresponding author. Tel./Fax: +81-58-293-2619, E-mail: koketsu@gifu-u.ac.jp.

reported and the most abundant in nature are ^{80}Se (49.6 %) and ^{78}Se (23.8 %). Selenium was predicted to be hazardous causing livestock poisoning [2] until it was recognized as an essential nutrient of animals and humans found in some selenoproteins in 1950s [3,4]. Schwarz and co-workers reported its ability to serve interchangeably with vitamin E in the prevention of vascular or muscular signs in experimental animals [5]. The metabolic basis of this nutritional function remained unclear, however, until it was discovered that the enzyme glutathione peroxidase (GPx) contained Se as an essential component of its catalytic center [6]. After that, several Se-dependent GPx forms [7-9] and other selenoenzymes and specific selenoproteins, namely, iodothyronine 5`-deiodineses, [10,11] thioredoxin reductase (TrxR), [12] plasma selenoprotein P, [13] and muscle selenoprotein W [14] were subsequent discovered. Each selenoprotein contains Se in the form of selenocysteine (SeCys), which is incorporated by the co-translational modification of transfer RNA-bound serine at certain loci coded by specific uracil-guanine-adenine codons [15,16].

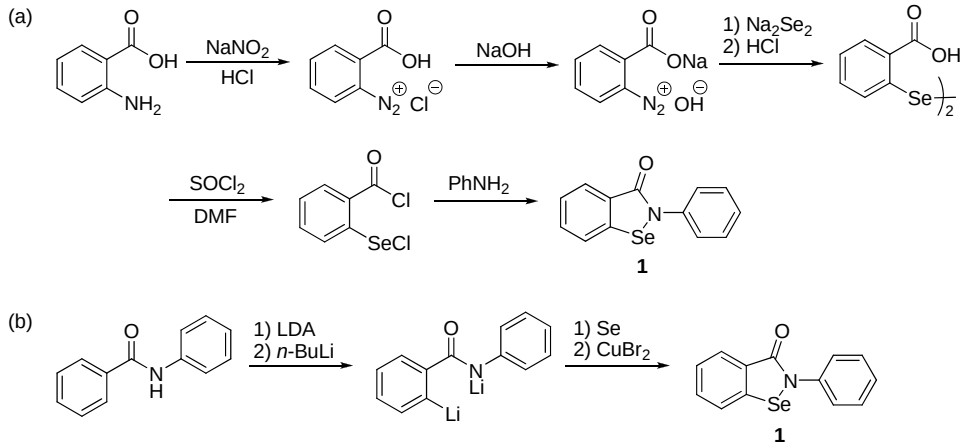
The beneficial effects of selenium in human health are strongly dependent on its concentration. The concentration range in which selenium is considered toxic or essential is very constricted. It has been estimated that the ingestion of foodstuffs with selenium content above 1 mg of Se/kg can induce toxicity, meanwhile a concentration below 0.1 mg of Se/kg leads to deficient status [17]. The main source of selenium in human beings is the diet. At present, the recommended value for adults is 55 μg of Se/day for both sexes.

The first report on synthesis of an organoselenium compound, diethyl selenide, was in 1836 [18]. However, the chemistry of organoselenium compounds has not been developed in comparison with that of organosulfur compounds because of the instability and strong toxicity of some Se-containing compounds. Recently, the synthetic study of organoselenium compounds is becoming increasingly interesting due to their unique reactivities and, potent and diversified biological activities. The structures of organoselenium compounds are closely related to those of analogues of sulfur compounds, but their properties often present marked difference. Development of selenating reagents is an active research area [19,20]. Interest in selenium-containing therapeutics has grown over last thirty years [21,22]. They already become indispensable in the field of medicinal chemistry. There are also some excellent books and reviews about pharmacology of organoselenium compounds [23-29]. Herein, we would like to discuss biologically significant selenium-containing heterocycles from the viewpoint of chemical structures.

2. Ebselen and its related compounds

Ebselen (2-phenyl-1,2-benzisoselenazol-3(2*H*)-one) called PZ 51 or DR3305 is an anti-inflammatory anti-oxidant selenium-containing heterocycle, which was first prepared in 1924, [30] that has been extensively investigated during the last decade. Particular interest in this drug resulted from the early observation that ebselen mimics GPx activities [31,32] in particular that of phospholipid hydroperoxide glutathione peroxidase [33]. Ebselen has been prepared by several methods. In the earliest approach 2,2`-diselenobis(benzoic acid) was converted to 2-chloroselenobenzoyl chloride, which was treated with aniline to give ebselen (Scheme 1, (a)) [34]. More useful advance

involves ortholithiation of benzanilide, subsequent insertion of selenium into benzanilide-derived dianion and cyclization of selenium-containing dianion to ebselen (Scheme 1, (b)) [35].



Scheme 1. Synthesis of Ebselen.

The discovery of the GPx-like activity of ebselen in 1984 has attracted the interest of many researchers [31,32]. The GPx, a mammalian selenoenzyme which catalyzes the reduction of hydroperoxides by glutathione, acts through an active site containing the essential selenocysteine residue. Its activity is due to a catalytic cycle involving different oxidation states of the selenium atom. Ebselen could act against oxidative stress in similar way as the GPx, in contrast to its sulfur analogue (PZ 25) which is almost devoid of this activity. In earlier work on the mechanism of the GPx-like activity of ebselen, Fischer and Dereu proposed, on the basis of their ^{77}Se NMR study [36], the functioning of two catalytic cycles (Fig. 1, Cycle A and B) dependent on whether the hydroperoxide (Fig. 1, Cycle A) or the thiol (Fig. 1, Cycle B) occurs in excess over the other reaction partner. On the other hand, later work of other groups has unequivocally established the transient formation of the selenol in aqueous systems containing glutathione [37,38]. In this way, Cycle C would be operative under the premise that both ebselen selenol and ebselen diselenide are required intermediates. However, owing to its high reactivity toward hydroperoxides, the selenol can also be directly converted to ebselen, thus closing Cycle D (Fig. 1) [39].

In contrast, ebselen does not react with diphenylpicrylhydrazyl (DPPH) which is reactive against potent free-radical scavengers [40]. The lack of radical-scavenging activity of ebselen is further substantiated by the observation that ebselen does not inhibit lipid peroxidation induced by free-radical initiators and that it does not protect α-tocopherol from co-oxidative destruction during this process (Table 1) [41]. By contrast, ebselen is a potent inhibitor of lipid peroxidation process induced by transition metals, e.g. in microsomes, [31] in mitochondria, [42] and with methyl linolate [41]. This type of lipid peroxidation is brought about by a Fenton-type reaction of the metal ion with traces of hydroperoxides forming an alkoxy radical and the higher valency state of the metal. Ebselen inhibits this process at its earliest stage by removing the hydroperoxides. The inhibition by ebselen of certain forms of lipid peroxidation is not obligatorily dependent on the presence of glutathione [31] indicating that the

hydroperoxide-reducing action rather than the GPx-like activity is responsible for the inhibition. Glutathione is however required in such *in vitro* systems in which the formation of hydroperoxy-lipid exceeds the concentration of ebselen available (Table 1). In this case, glutathione is needed to regenerate the ebselen from ebselen selenoxide (Fig. 1, Cycle A). Mugesh and co-workers reported the anti-oxidant activities of ebselen on several oxidation assay systems [43]. According to above, ebselen shows significant GPx-like activity; the GPx-like activity of ebselen not only depends on the reactivity of the selenol intermediate towards hydroperoxides, but also depends on the reactivity of the selenenyl sulfide intermediate towards thiols [44]. Although there is no thiol present in the horseradish peroxidase (HRP) inhibition experiment, ebselen demonstrates its strong activity. In addition, the anti-oxidant potency of ebselen is superior in the γ-radiation-induced lipid peroxidation in liposomes and singlet oxygen quenching assay.

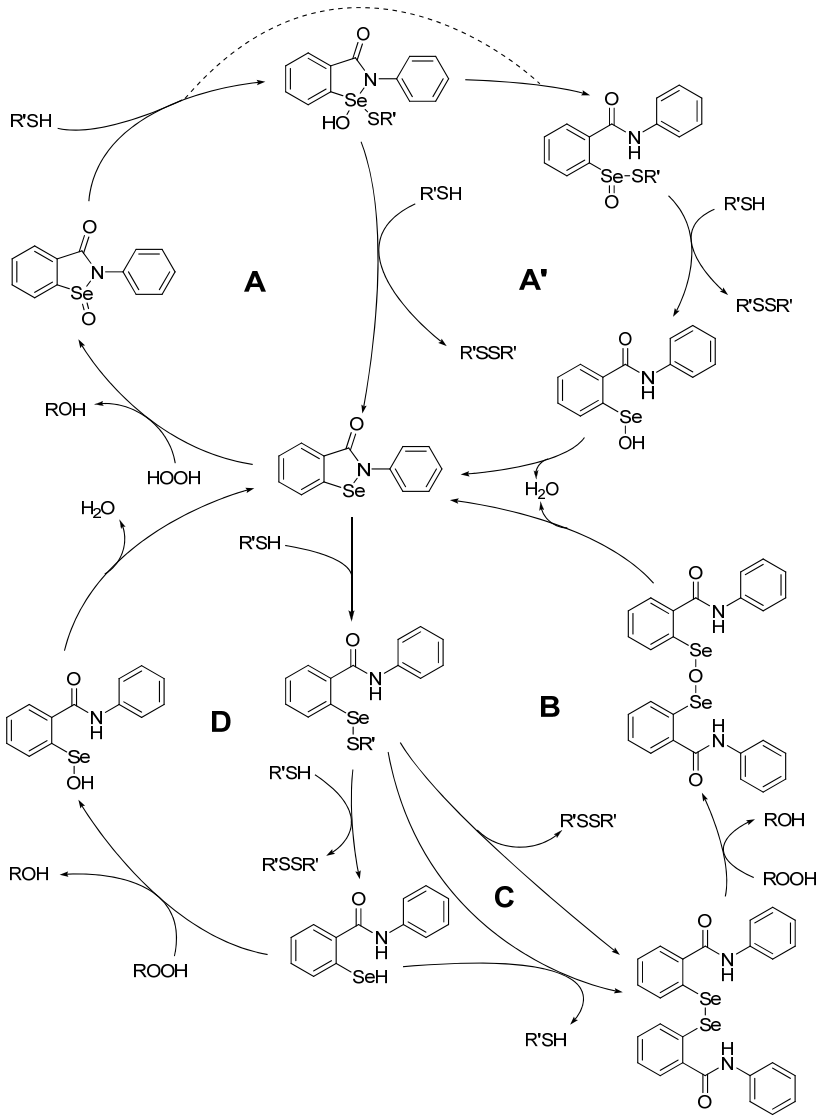


Fig. 1. Interconversions of ebselen and its metabolites by reaction with hydroperoxides. and thiols and reaction cycles (A–D).

Table 1
Anti-oxidant profile of ebselen [43]

	$^1O_2$+substrate k (x10^6 $M^{-1}s^{-1}$)[a]	Lipid peroxidation IC_{50} (μM), 280 Gy[b]	GPx activity K_m (x10^{-3})[c]	GPx activity V_{max} (μMmin^{-1})[c]	HRP inhibition IC_{50} (μM)[d]
Ebselen	4.16 ± 0.12	25	13.15	182.9	16.9 ± 1.4

Assay conditions: [a]$^1O_2$ generated by hypocrellin-A, ebselen (0.1-4 mM), [b]phosphatidyl choline liposomes, thiobarbituric acid reactive sucstances (TBARS) usinf 15 % w/v trichloroacetic acid, 0.375 % w/v TBA, 0.25 N HCl, 0.05 % w/v BHT, [c]glutathione reductase (0.3 U/ml), NADPH (0.25 mM), glutathione (0.5-6 mM), ebselen (0.025 mM), hydroperoxide (1mM), [d]HRP enzyme (70 nM) mixed with 25 μM $ABTS^{2-}$, ebselen (0.06-0.1 mM), hydroperoxide (10 μM).

Ebselen is a multiple enzyme inhibitor, e.g. against lipoxygenases, [45-47] NADPH oxidase, [48] H^+/K^+-ATPase,[47,49] nitric oxide synthases, [50,51] and prostaglandin H synthase [46,52]. In many cases the molecular mechanism of the inhibitory effects of ebselen may be a blockade of thiol groups essential for structure and activity of these enzymes. Furthermore, it shows a wide range of biological activities. One grand review of pharmacological actions of ebselen has been written in the past by the German chemist Schewe [53].

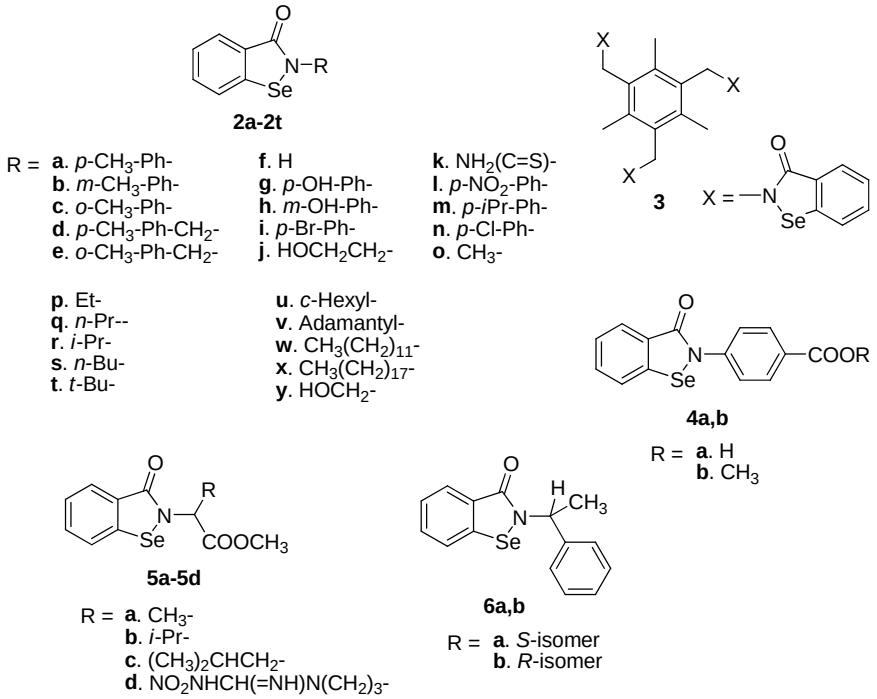


Fig. 2. Chemical structures of synthesized analogues of Ebselen.

Its poor solubility remains a problem for optimal therapeutic development. In order to enhance its solubility and to increase its activity, research has focused on modifications

of the structure of ebselen (Fig. 2). Based on the ebselen structure, Hsu and co-workers synthesized five ebselen derivatives **2a-2e** and screened for their GPx-like activity. All the compounds tested displayed similar significant activity, which are slightly higher than that of ebselen (Table 2) [54]. Bhabak and Mugesh also prepared ebselen derivatives **2f-2k**, **3** and evaluated their anti-oxidant activity [55]. They exhibited excellent catalytic activity with glutathione, and the activities of **2g**, **2h**, **2j**, **2k**, and **3** were much higher than that of ebselen (Table 3). The lower catalytic activity of **2f** suggests that a substitution at the nitrogen is required for high GPx activity. The tris-ebselen compound **3** exhibited high GPx activity, although the initial rates were only two times higher than ebselen (Table 3). This was likely caused by the steric hindrance of the relative orientation of three ebselen units. The inhibitory effects of the derivatives **2l** and **2m** have been demonstrated on 15-LOXs [46]. The carboxylated analogue **4a** is an inhibitors of constitutive endothelial NOS (ecNOS) [50-51,56]. Further, as an extension of these studies several ebselen analogues **4b**, **5a-5d**, **6a**, and **6b** have also been synthesized and evaluated for their inhibitory properties in rabbit aortic rings (Fig. 2) [57]. The observed difference in the activity of two enantiomers **6a** and **6b** may be due to the stereospecific interactions between the inhibitor and the enzyme. The *p*-chloro analogue **2n** exhibited strong inhibitory activity against the growth of fungi *Saccharomyces cerevisiae* and *Candida albicans* strains [58]. Different *N*-substituted analogues of ebselen **2j** and **2o-2y** were designed as anti-viral and anti-microbial agents [59]. The majority of the compounds tested were highly active against Gram-positive bacteria strains, particularly *Stalyphylococcus aureus*, having MIC values in a range of 2.0–32.0 μg/ml, close to positive controls such as ebselen and penicillin G (MIC = 1.0 μg/ml). Generally, the compounds tested were inactive or weakly active against Gram-negative bacteria strains. Only **2J** and **2y** having hydroxyl group at 2-position of heterocyclic ring were moderately active against *Escherichia coli*. Strong fungicidal activities were shown by **2o-2x** substituted at 2-position with alkyl groups, e.g. against *C. albicans* (MIC = 1.0–3.0 μg/ml), *Aspergillus niger* (MIC = 8.0–28.0 μg/ml).

Table 2

GPx-like activity of ebselen and its analogues [54]

	GPx-like activity (relative to ebselen)[a]		GPx-like activity (relative to ebselen)[a]
Ebselen	1.00	**2c**	1.17
2a	1.36	**2d**	1.60
2b	1.47	**2e**	1.60

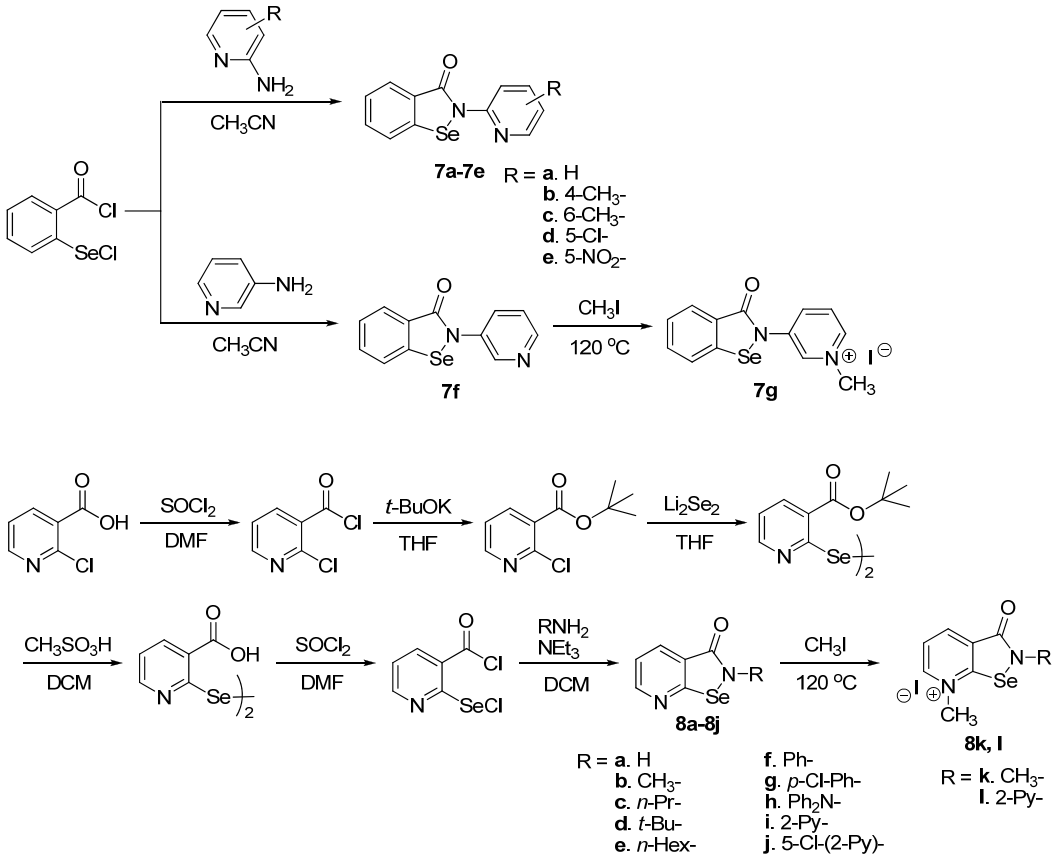
Assay conditions: [a]The consumption of NADPH upon addition of H_2O_2 in the absence of the compounds tested was 0.8 μM/min and the consumption of NADPH for ebselen was 10.9 μM/min.

Table 3

Initial rates v_0 for the reduction hydroperoxides and organic peroxides of ebselen and its analogues [55]

	Initial rates v_0 (μM/min)[a]		
	H_2O_2	*t*BuOOH	Cum-OOH
Ebselen	140.3 ± 1.6	86.1 ± 1.0	88.2 ± 0.1
2f	103.0 ± 0.5	59.0 ± 2.4	87.3 ± 2.4
2g	278.0 ± 1.3	169.1 ± 2.9	266.8 ± 1.7
2h	257.7 ± 0.3	142.6 ± 0.7	231.8 ± 2.7
2i	71.2 ± 0.8	29.8 ± 0.6	45.8 ± 2.4
2j	179.1 ± 1.7	124.2 ± 1.3	143.4 ± 0.4
2k	337.8 ± 0.1	216.1 ± 2.9	330.7 ± 2.4
3	253.6 ± 1.3	177.0 ± 2.5	213.9 ± 2.0

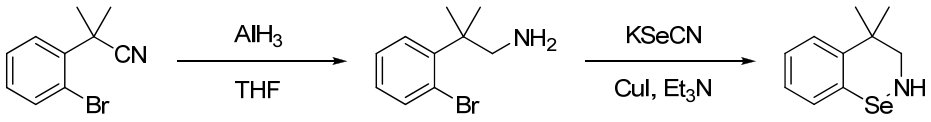
Assay conditions: [a]glutathione (2 mM), NADPH (0.4 mM), glutathione reductase (1 U), peroxide (1.6 mM), EDTA (1 mM), phosphate buffer (100 mM), and tested compound (80 μM).



Scheme 2. Synthesis of aza-analogues of ebselen.

Aza-analogues of ebselen were designed as selenium-containing anti-viral and anti-microbial agents [60]. 2-Chloroselenobenzoyl chloride reacting with various

aminopyridines produced 2-(2-pyridyl) and 2-(3-pyridyl)benzisoselenazol-3(2*H*)-ones **7a-7g** (Scheme 2) [61]. The strategy for synthesis of 7-azabenzisoselenazol-3(2*H*)-ones **8a-8l** was based on the conversion of 2-chloronicotinic acid into 2-(cloroseleno)nictinoyl chloride and finally on the tandem acylation-selenylation of the primary amino group of aminoalkanes and aminoarenes (Scheme 2). Quaternary salts of **8** were prepared by the reaction with methyl iodide. All aza-analogues of ebselen and their quaternary salts were tested against pathogenic bacteria, yeasts, and filamentous fungi. The broadest spectrum of activity against tested microorganisms was observed for **8b** having MIC values in the range of 2.0–32.0 μg/ml. The biological response for the Gram-positive and Gram-negative bacteria, and yeasts *C. albicans* was substantially stronger than ebselen. The compound **8b** was active against filamentous fungi strains such as *A. niger*, *Penicillium chrysogenum*, and *P. citrium* more resistant compared with ebselen.



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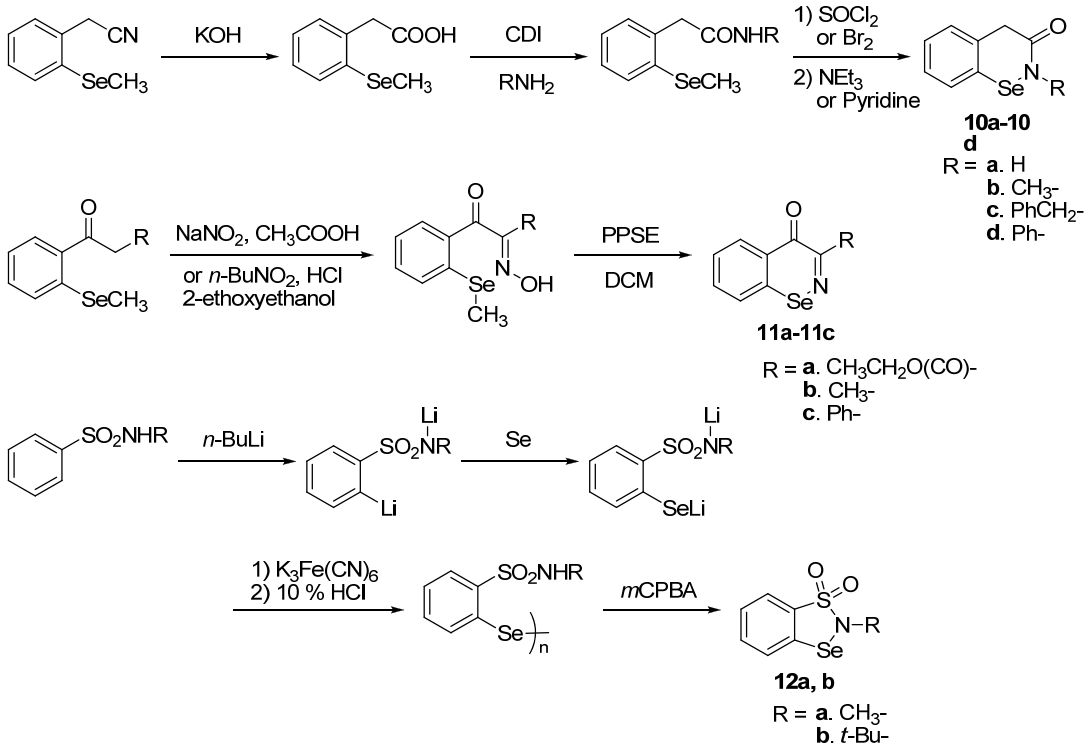
Scheme 3. Synthesis of 3,4-dihydro-4,4-dimethyl-2*H*-1,2-benzoselenazine.

The candidate drug was 3,4-dihydro-4,4-dimethyl-2*H*-1,2-benzoselenazine (ALT-2074; formerly BXT-51072), orally active, catalytic mimic of the GPx which is being developed for the treatment of inflammatory disorders characterized by the involvement of reactive oxygen species (ROS). The simple preparation has been proposed by Erdelmeier and co-workers [62]. Starting from 2`-bromophenyl-2-methylpropionitrile, they accessed the important intermediate 2-bromo-β,β-dimethylbenzeneethanamine on a multigram scale in one step. Reaction of the benzeneethanamine with potassium selenocyanate in the presence of copper(I) iodide and triethylamine gave the selenazine **9** (Scheme 3). This compound exhibited 2-fold higher GPx activity than that of ebselen [63]. Furthermore, it inhibited tumor necrosis factor α (TNF-α)-induced expression of the adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) by endothelial cells [64]. Interestingly, such effects were not observed with ebselen. Selenazine **9** was an inhibitor of human cytochrome P450 3A (CYP3A), with the IC_{50} value of 2.0–2.6 μM *in vitro*. The *in vivo* study also indicated that it inhibits CYP3A metabolism [65].

The ability of Se-containing heterocycles to behave as ebselen analogues with respect to biological activities looks promising in this class of compounds. In other words, the important concepts for ebselen analogue's synthesis are (1) a selenium-$C_{aromatic}$ carbon bond, to avoid selenium release and maintain the low toxicity of ebselen, (2) a selenium-nitrogen bond, which is responsible for the GPx-like activity, and (3) a nitrogen-carbonyl bond to stabilize the selenamide structure. The synthesis of 2*H*-3,4-dihydro-1,2-benzoselenazin-3-ones **10a-10d** which are six-membered homologues of ebselen has been performed (Scheme 4) [66]. Renson and co-workers started from *o*-methylselenophenylacetonitrile, alkaline hydrolysis of the nitrile and then carbonyldiimidazole (CDI) method gave the amides. The amides were cyclised into the corresponding compounds **10a-10d** by methods of halogenation to a selenylhalide and dehydrohalogenation with a base such as triethylamine or pyridine [67]. Other

six-membered homologues of ebselen 4*H*-benzo[*e*]-1,2-selenazin-4-ones **11a-11c** were designed and synthesized [68]. The key step of this synthesis approach is cyclization of oximes *via* Se-demethylation using trimethylsilyl polyphosphate (PPSE) [69]. 2-Alkyl 1,3,2-benzothiaselenazole 1,1-dioxides **12a** and **12b** are provided by cyclization of 2,2`-diselenobis(*N*-alkylbenzenesulfonamide) using 3-chloroperoxybenzoic acid (*m*CPBA) (Scheme 4) [70].

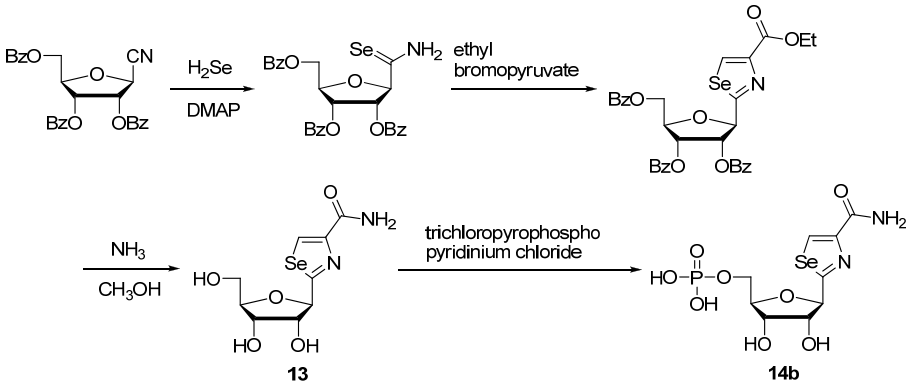


Scheme 4. Synthesis of homologues of ebselen and 2-alkyl 1,3,2-benzothiaselenazole 1,1-dioxides.

3. Selenazofurin and its related compounds

Selenazofurin (2-β-D-ribofuranosylselenazole-4-carboxamide), which has pronounced anti-tumor activity in animals and broad spectrum *in vitro* anti-viral activity, [71] is the selenium analogue of tiazofurin synthesized in 1983 by Srivastava and Robins [72]. They developed the synthetic route similar to the preparation method of tiazofurin [73]. Treatment of the precursor, 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-1-carbonitrile [74,75] with hydrogen selenide, with 4-dimethylaminopyridine (DMAP) as a catalyst, provided 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonoselenoamide as a foamy material. The corresponding selenoamide was treated with ethyl bromopyruvate to give ethyl 2-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)selenazole-4-carboxylates as a mixture of α,β-anomers, which were readily separated by silica gel column chromatography. Selenazofurin was obtained by the deprotection and amination reaction of the β-anomer with mathanolic ammonia. They further prepared its 5`-phosphate using

trichloropyrophosphopyridinium chloride, [76] which is generated in situ *via* the treatment of phosphoryl chloride with pyridine and water in acetonitrile (Scheme 5). Selenazofurin and its 5`-phosphate were cytotoxic toward P388 and L1210 cells in culture and effective against Lewis lung carcinoma in mice. Selenazofurin exhibited an $IC_{50}$ of 0.3 μM for P388 cells and 0.4 μM for L1210 cells, and 5-fold more potent than tiazofurin. 5`-phosphate analogue of selenazofurin was as cytotoxic (IC_{50} = 0.39 μM) to L1210 cells as selenazofurin itself but was approximately 8-fold more potent than tiazofurin 5`-phosphate. Selenazofurin has significant activity against P388 and Ridgeway osteogenic sarcoma *in vivo* [72,77]. In the tumor inhibition studies, a daily dose of selenazofurin for 4 days was effective.



Scheme 5. Synthesis of selenazofurin and its phosphate.

Selenazofurin is 5–10-fold more potent than tiazofurin in several *in vitro* and *in vivo* anti-tumor screenings [71,72,77-80]. Both the anti-proliferative and maturation-inducing effects of these nucleoside analogues appear to be due to inhibition of inosine 5`-monophosphate dehydrogenase (IMPDH), a rate-limiting enzyme of *de novo* guanine nucleotides biosynthesis. The IMPDH, which catalyzes the nicotinamide adenine dinucleotide (NAD)-dependent conversion of inosine 5`-monophosphate (IMP) to xanthosine 5`-monophosphate (XMP), was significantly increased in highly proliferative cells. Inhibition of this enzyme results in a decrease in guanosine triphosphate (GTP) and deoxy-GTP biosynthesis, producing inhibition of tumor cell proliferation [81]. Selenazofurin is metabolized in sensitive tumor cells to the corresponding selenazole-4-carboxamide-adenine dinucleotide (SAD) [82]. The dinucleotide, which is a potent noncompetitive inhibitor of IMPDH, binds to the NAD active site of the enzyme. Crystallographic studies of selenazofurin have demonstrated close contacts between the selenazole selenium and the furanose oxygen. A significant Se-O interaction would constrain rotation about the *C*-glycosidic bond in SAD. This in turn would influence specificity of bonding of selenazofurin metabolites to the target enzyme. The nonbonded interaction clearly has important biological implications [83-84]. IMPDH inhibitory activity of 5`-phosphate and dinucleotide analogues of tiazofurin and selenazofurin has been reported [85]. Table 4 indicates that the dinucleotide analogues **14c-14f** are more potent inhibitors than the 5`-phosphate analogues **14a** and **14b**. Among these, adenine-containing analogues **14c** and **14d** exhibited excellent activity.

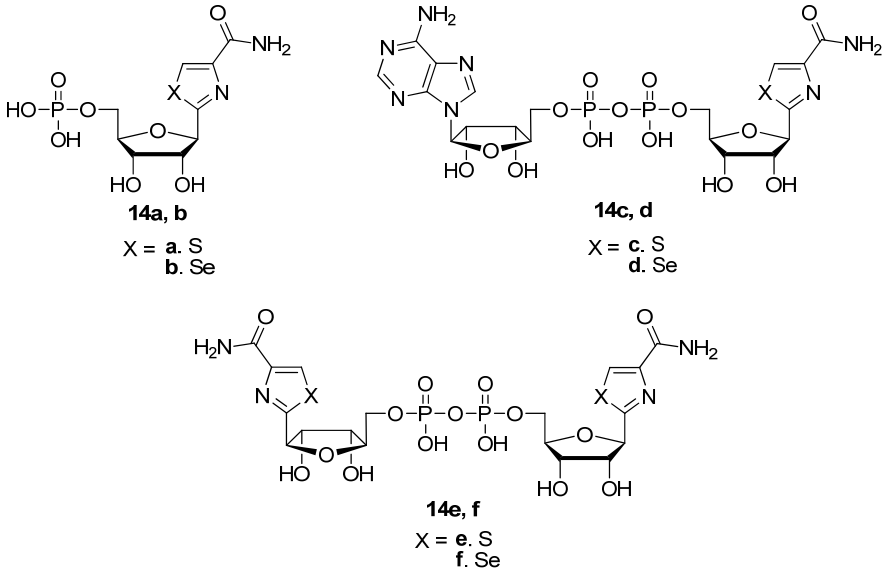


Fig. 3. Chemical structures of 5`-phosphate and dinucleotide analogues of tiazofurin and selenazofurin.

Table 4

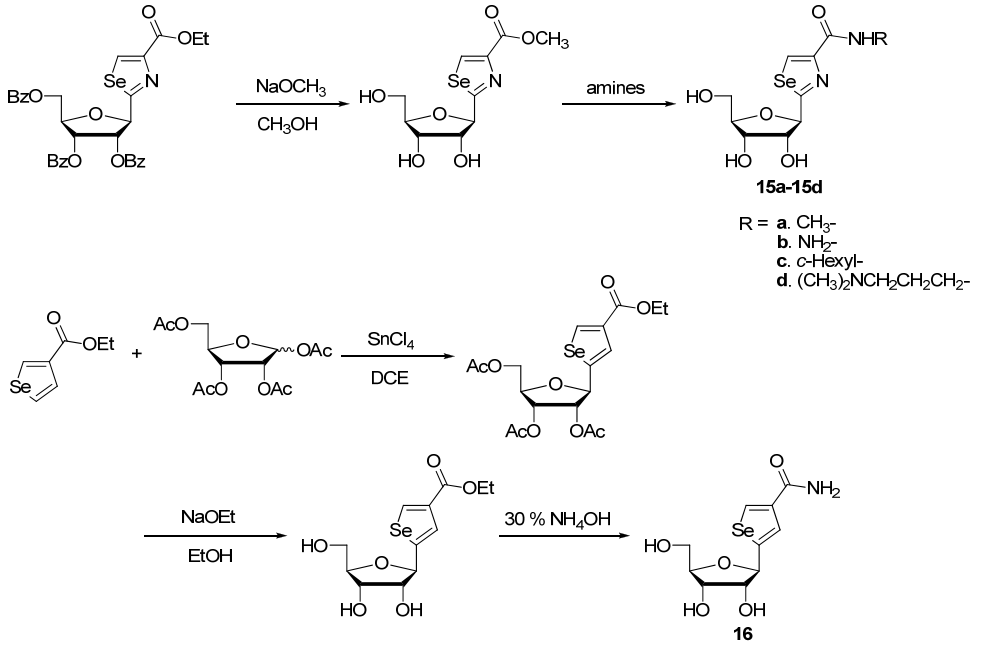
IMPDH inhibitory activity of 5`-phosphate and dinucleotide analogues of tiazofurin and selenazofurin [85]

	IMPDH inhibition K_i (μM)	
	IMP	NAD
14a	265	405
14b	170	470
14c	0.13	0.24
14d	0.05	0.04
14e	140	370
14f	190	240

In general, nucleoside analogues are an important class of compounds in the treatment of various viral diseases. Typically, these compounds are prodrugs that must be converted to nucleotide metabolites to exert their anti-viral activity. Most viruses do not express the enzymes that are necessary for activation of nucleoside analogues. Therefore, these compounds must be activated by the host purine or pyrimidine metabolic enzymes to nucleotides that can inhibit viral replication [86]. Although slenazofurin, a synthetic nucleoside analogue, is a potent broad spectrum anti-viral agent, much more is known about the metabolism and mechanism action of selenazofurin because of its development as an anti-tumor agent. Selenazofurin is thought to demonstrate anti-viral activities by inhibiting of IMPDH in the GTP biosynthetic pathway like another nucleoside anti-virals [83,87-89].

Selenazofurin is a potent anti-viral agent *in vitro*, inhibiting the replication of such diverse viruses as paramyxoviruses, reoviruses, poxviruses, herpesviruses, togaviruses, bunyaviruses, arenaviruses, picornaviruses, adenoviruses, and rhabdoviruses [71-90]. In addition, selenazofurin demonstrates its significant anti-influenza A and B activities (IC_{50} = 25 and 19 μM, respectively) *in vitro* [91,92]. Gilbert and co-workers have indicated that triphosphate in the selenazofurin molecule may inhibit the *in vitro* elongation of capped primer fragments by the influenza virus transcriptase complex. However, the *in vivo* study using mice was not satisfactory. It is possible that selenazofurin was metabolized to an inactive or to a more toxic material in the mouse, or was inadequately absorbed [93]. In other *in vivo* studies, selenazofurin also proved to be inactive or toxic in animal models [94-95].

N-Substituted amide derivatives of selenazofurin were synthesized through aminolysis with several amines instead of ammonia (Scheme 6) [75]. IC_{50} values of the amide derivatives **15a-15d** against *in vitro* L1210 cells were greater than 100 μM as compared with that of selenazofurin. The **15a** and **15b** were not active against P388 leukemic mouse model at 200 mg/kg [77]. The synthetic and biological evaluation of selenophenfurin, in which the selenazole ring is replaced into a selenophene heterocycle, has been performed [96]. Direct *C*-glycosylation of ethyl selenophene-3-carboxylate with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose was carried out under Friedel-Crafts conditions as a key step. The corresponding selenophenfurin was obtained by deacetylation using sodium ethoxide and then amination with ammonium hydroxide (30 %). Selenophenfurin is an anti-proliferative against a number of leukemia, lymphoma, and solid tumor cell lines at concentrations similar to those of selenazofurin but was more potent than the thiophene and thiazole analogues thiophenfurin and tiazofurin. Incubation of K562 cells with selenophenfurin resulted in inhibition of IMPDH (76 %) and an increase in IMP pools (14.5-fold) with a concurrent decrease in GTP levels (58 %).

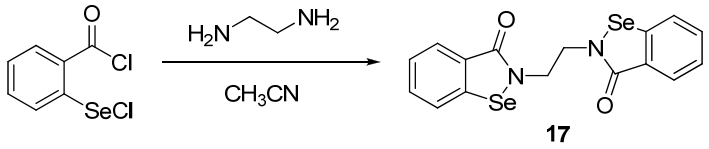


Scheme 6. Synthesis of *N*-substituted amide derivatives of selenazofurin and a

selenophenfurin.

4. Ethaselen

As one of the anti-tumor drugs, ethaselen (1,2-[bis(1,2-benzisoselenazolone-3(2*H*)-ketone)]ethane) **17** called BBSKE has been extensively investigated by Zeng in China [97]. In both *in vitro* and *in vivo* studies, the compound **17** demonstrated significant anti-tumor effects with slight toxicity and immune regulating characteristics in several tumor models. A simple preparation has been proposed by Młochowski and co-workers [98]. The strategy for synthesis of ethaselen was similar to the synthesis of ebselen and its analogues reported earlier [61]. The reaction of 2-chloroselenobenzoyl chloride with ethylenediamine was carried out under standard conditions to produce the corresponding ethaselen (Scheme 7).



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Scheme 7. Synthesis of Ethaselen.

The anti-tumor effect of ethaselen is due to its action on thioredoxin reductase (TrxR) [99]. TrxR is a NADPH-dependent SeCys-containing flavoenzyme. It catalyzes the reduction of oxidized Trx. The Trx system (NADPH, TrxR/Trx) plays several key roles in DNA synthesis and activation of transcription factors that regulate cell growth [100]. Studies have shown that expressions or activities of TrxR/Trx system have been up-regulated in a variety of human primary tumors comparing to levels in its equivalent normal tissue [101-103]. Ethaselen could inhibit TrxR activity and many kinds of tumor cell proliferation *in vitro*, including liver cancer cell Bel-7402, leukemia cell HL-60 and K562, cervical cancer cell HeLa, stomach cancer cell BGC 823, lung cancer cell A549 and Calu-3, prostate cancer cell DU-145 and PC-3, and pharyngeal cancer cell KB (IC_{50} values at 72 h in the range of 2.0–17.6 μM) [97,99,104-108]. Moreover, Zeng and co-workers analyzed three apoptosis proteins, including Bcl-2, Bax, and caspase-3, among five kinds of human cancer cell lines (A549, HeLa, Bel-7402, BGC 823, and KB) [105]. The results strongly proved that ethaselen could induce tumor cells apoptosis. It is clear that the TrxR inactivation of ethaselen correlates with cell death/apoptosis in the cells investigated because the TrxR/Trx level is associated with tumor growth, apoptosis, and resistance of chemotherapy [109-111]. It has been suggested that the mechanism is related to inducing mitochondria-dependent apoptosis in A549 cells probably through suppressing the TrxR-Trx-nuclear factor-κB (NF-κB) pathway [99]. The *in vivo* studies by Li and co-workers provided experimental evidence that ethaselen has an inhibitory action on growth of Tca8113 tongue cancer cells in nude mice [106]. Recently, the effects of ethaselen and cisplatin (*cis*-diamminedichloroplatinum II, DDP) combination therapy on human A549-grafted nude mouse model was reported [112]. Compared to single drug administration, the combination therapy showed significantly reduced tumor size (presumably due to a synergistic effect) and no obvious toxic damage (both in terms

of body weight maintenance and liver/kidney damage).

Hence, ethaselen has great promise and has now entered Phase I clinical trials in China. Ethaselen appears to be an excellent candidate for development of a new anti-tumor and anti-cancer drug [113]. See more detail review article for the ethaselen [114].

5. Amselamine

The biogenic amine histamine mediates its effects by four histamine receptor (HR) subtypes, designed H_1 (H_1R), H_2 (H_2R), H_3 (H_3R), and H_4 receptors (H_4R), all belonging to family A of G-protein coupled receptors (Fig. 4) [115]. In these receptors, H_2R are mainly expressed in gastric parietal cells, the heart, neurons, and immune cells and play a crucial physiological role in stimulating gastric acid secretion [116,117]. Thus, H_2R-antagonists such as cimetidine and ranitidine are first-choice drugs for the treatment of gastric and duodenal ulcer and gastroesophagal reflux disease. On the other hand, studies directed toward selective H_2R-agonist were less successful until the discovery of dimaprit in 1970s [118].

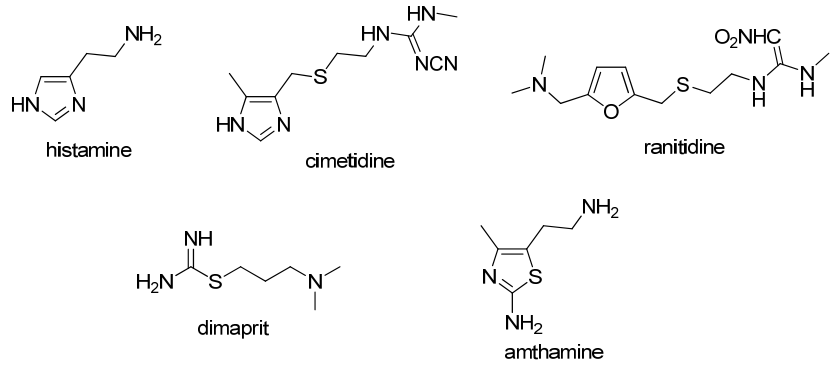
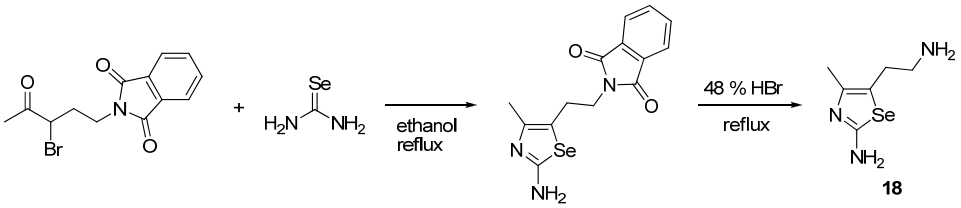


Fig. 4. Chemical structures of histamine, H_2R-antagonists and –agonists.

For a long time the possibility of a tautomeric shift of the ligand, as can be very easily achieved in the imidazole structure of histamine, was thought to be a structural requirement for the stimulation of H_2R.[119] Meanwhile, Timmerman and co-workers provided evidence that non-tautomeric structures can be also H_2R-agonists [120]. One of these compounds is amthamine, which is the most active compound of the thiazole series (Fig. 4). Later it was reported that amselamine (2-amino-5-(2-aminoethyl) -4-methyl-1,3-selenazole) **18**, a selenium analogue of amthamine, is a more potent H_2R-agonist than amthamine and histamine [121]. Amselamine **18** was prepared as indicated in Scheme 8. Phthalimidobromopentanone was condensed with selenourea in refluxing ethanol. Subsequently, the corresponding amselamine was obtained by hydrolysis of the phthalimidoselenazole in refluxing 48 % HBr.

Amselamine **18** is a potent and selective H_2R-agonist [122-124]. Because the selenazole ring of amselamine is somewhat more basic than the thiazole ring of amthamine, it may be expected that amselamine **18** has a slightly higher affinity for H_2R than histamine. However, the different activities of amselamine **18** and amthamine are still ambiguous. The two compounds should exert almost equal affinities for the H_2R on

CHO cells [121,125,126].

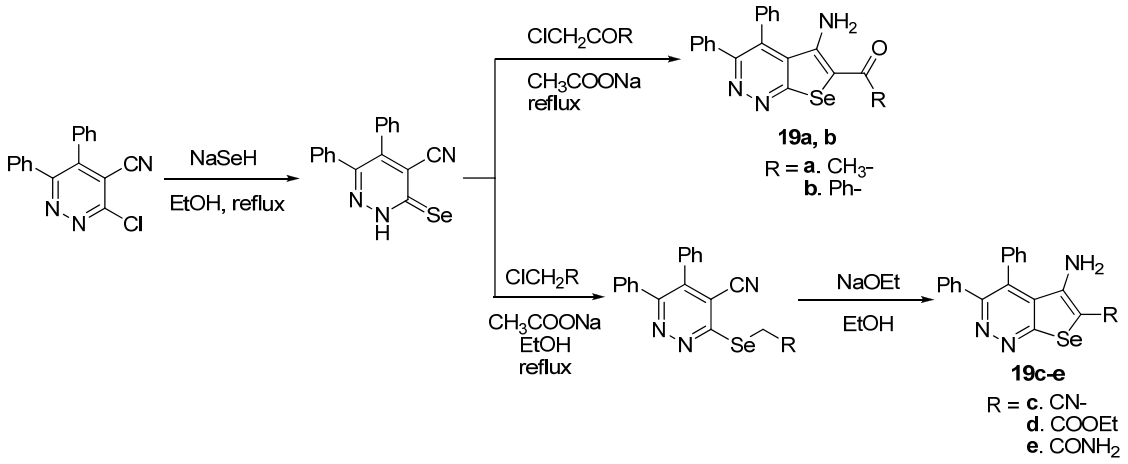


Scheme 8. Synthesis of amselamine.

6. Se-containing 5-membered rings

In recent years, many kinds of Se-containing 5-membered ring compounds have been vigorously studied in organic synthesis and also medicinal chemistry. Here, we discuss these compounds categorized into selenophenes, selenazolidines, selenazoles, and selenadiazoles by the chemical structures.

Selenophene is a 5-membered cyclic compound containing one Se atom and two double bonds. Among chalcogenophenes, selenophene plays an important role in organic synthesis because of its electrical property and stability. The preparation of the selenophene from selenoamide vinylogue was proposed in 1976 by Liebscher and Hartmann using an electrophile reagent [127]. Selenophene has drawn the attention of researchers in view of its interesting biological activities.

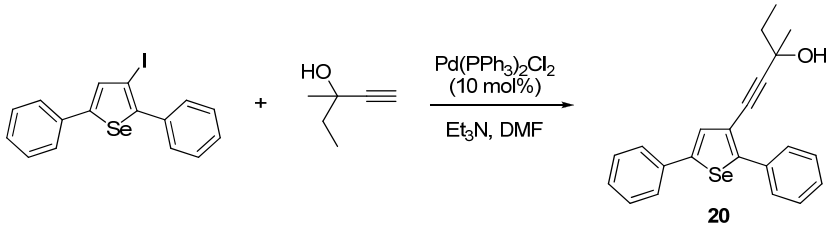


Scheme 9. Synthesis of 3-amino-4,5-diphenylselenolo[2,3-*c*]pyridazines.

The synthesis and anti-inflammatory activity of 3-amino-4,5-diphenylselenolo[2,3-*c*]pyridazines **19** have been reported [128]. The key intermediate 4-cyao-5,6-diphenylpyridazine-3(2*H*)selenone was prepared by the reaction of 3-chloro-4-cyano-5,6-diphenylpyridazine with sodium hydrogenselenide in refluxing ethanol. The reaction of the intermediate with chloroacetone or phenacyl bromide in the presence of sodium acetate as a basic catalyst afforded 2-acyl-3-amino-4,5-diphenylselenolo[2,3-*c*]pyridazines **19a** and **19b**. The corresponding

2-cyano, 2-ethylester, or 2-amide derivatives **19c-19e** were prepared by the reaction of the intermediate with chloroacetonitrile, ethyl chloroacetate, or chloroacetamide and then Thorpe-Ziegler cyclization (Scheme 9). Among these, compound **19c** showed the most active anti-inflammatory behavior.

3-Iodoselenophene derivatives undergo direct Sonogashira cross-coupling reactions with several terminal alkynes in the presence of a catalytic amount of $Pd(PPh_3)_2Cl_2$ with triethylamine as a base under cocatalyst-free conditions [129]. 1-(2,5-Diphenylselenophen-3-yl)pent-1-yn-3-ol **20** was prepared employing this useful method (Scheme 10). The compound **20** presents anti-convulsant and anti-oxidant effects in 21-day-old rats in a pilocarpine model of seizures. This study confirmed the anti-convulsant activity of compound **20** and the drug's ability in reducing the oxidative stress in the pilocarpine model [130]. The compound **20** has hepatoprotective effect against acute liver injury induced by D-galactosamine (D-GalN) and lipopolysaccharide (LPS) in rats by the mechanism that involves its anti-oxidant activity [131]. Compound **20** at a dose range of 5–50 mg/kg was especially potent and produced systemic anti-hyperalgesic and anti-nociceptive actions in mice [132]. The compound **20** might be of potential interest in the development of a new clinically relevant drug for the management of pain.



Scheme 10. Synthesis of 1-(2,5-diphenylselenophen-3-yl)pent-1-yn-3-ol.

2,5-Bis(5-hydroxymethyl-2-selenienyl)-3-hydroxymethyl-*N*-methylpyrrol (D-501036) **21** which is a diselenophene derivative exerts substantial anti-tumor activity both *in vitro* and *in vivo* (Fig. 5) [133]. Compound **21** is highly toxic to cancer cells but spares normal cells. The **21** is active against tumor cell lines that are resistance to other anti-cancer drugs as a consequence of overexpression of P-glycoprotein. The **21** induces cellular apoptosis though the p53-associated mitochondrial pathway [134]. 1-Benzyl-3-(5-hydroxymethyl-2-furyl)selenolo[3,2-*c*]pyrazole **22** was evaluated for cytotoxicity with a panel of NCI human cancer cell lines [135,136]. The mode of action of this compound **22** seems to differ from those of the 175 anti-cancer agents. Compound **22** may be developed further as a new candidate for treatment of non-small cell lung and renal cancers [137]. One of the selenosartans **23**, a selenium derivative of milfasartan, exhibits its potent angiotensin type 1 (AT_1) receptor antagonist property [138]. 4-Hydroxyphenyl and C5`-aminoalkylamide substituted selenophene derivatives of oxindole **24a-24e** with the IC_{50} value of subnanomolar range possess the excellent inhibitory activities against checkpoint kinase-1 (CHK1) enzyme (Fig. 5) [139].

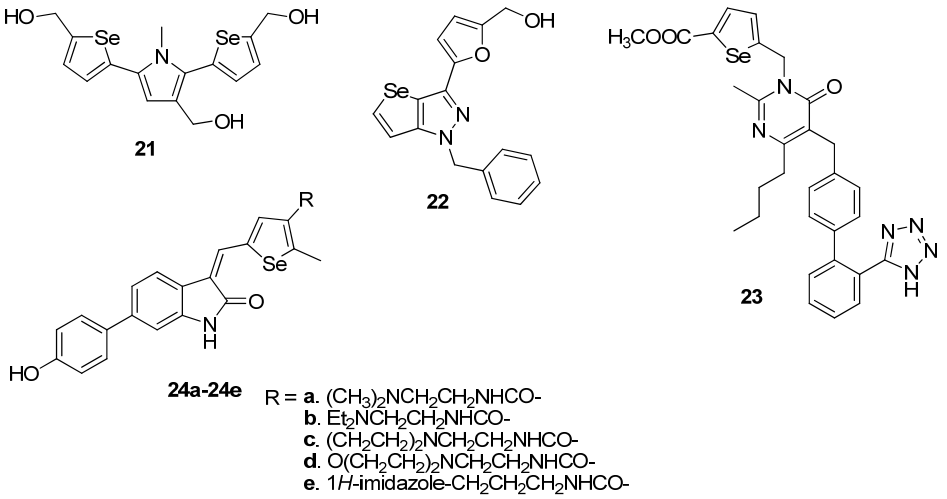
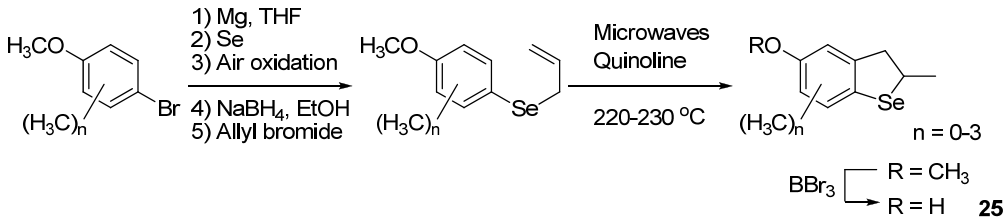


Fig. 5. Chemical structures of bioactive selenophene derivatives.

A series of 2,3-dihydrobenzo[*b*]selenophen-5-ols was prepared by subjecting suitably substituted allyl 4-methoxyphenyl selenides to microwave-induced seleno-Claisen rearrangement/intramolecular Markovnikov hydroselenation followed by boron tribromide-induced *O*-demethylation (Scheme 11) [140]. 2-Methyl-2,3-dihydrobenzo[*b*]selenophene-5-ol **25**, having the calculated log *P* value of 2.9, is a catalytic anti-oxidant in a two-phase lipid peroxidation system [141]. A mechanism of catalysis involving electron transfer from thiol to phenoxyl radical followed by proton transfer and dimerisation of thiyl radicals is shown in Fig. 6 [142]. The compound **25** quenched 2,2`-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS)-radicals and scavenged reactive oxygen and nitrogen species more efficiently than Trolox for neutrophils and phorbol 12-myristate 13-acetate (PMA)-stimulated macrophages, with good safety [143]. It would be a candidate for future drug development for prevention or treatment of disorders caused by or involving free radical-mediated or oxidative tissue damage.



Scheme 11. Synthesis of 2,3-dihydrobenzo[*b*]selenophen-5-ols.

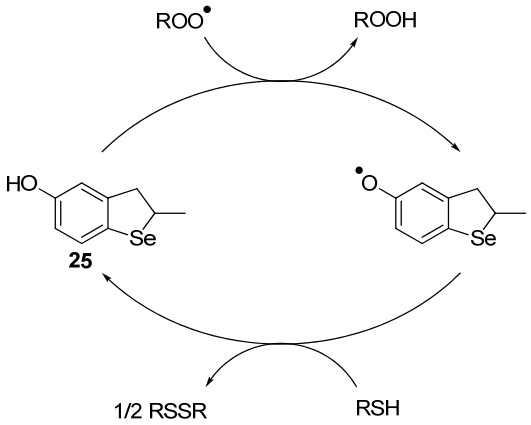


Fig. 6. Proposed mechanism for the catalytic action of 2-methyl-2,3-dihydrobenzo[*b*]selenophen-5-ol.

Selenazolidine rings contain one Se atom and one N atom. In 1972, a series of papers reported the production of selenazolidines from selenocysteamine, selenocysteine (SeCys), and selenopenicillamine (β,β-dimethylselenocysteine) by Drageut and Renson [144-147]. This work focused on exploring the mechanism of selenazolidine formation starting from hydrogen selenide and aziridine derivatives. Later work outlined the synthesis of selenaproline (selenazolidine-4-carboxylic acid), and its study as an inhibitor of protein synthesis [148,149].

The class of selenazolidine-4*R*-carboxylic acids was designed to release SeCys either enzymatically or though spontaneous hydrolysis (Fig. 7) [150]. In particular, an SeCys prodrug approach was conceived as a way to supply the supranutritional selenium requirement necessary for cancer chemopreventive activity without toxicity [151]. Of three selenazolidine-4*R*-carboxylic acids, prodrugs **26a**-**26c** reduced the number of lung adenomas that developed in four months following tobacco-derived nitrosamine (NNK) administration in mice [152]. Other prodrugs **26d**-**26g** also possessed chemopreventive activity in the same model [153]. Dependent on the nature of the 2-substituent, the chemopreventive activity can arise from changes elicited in the pre- or post-initiation period. The prodrug **26d** demonstrated its activity through both pre- and post-initiation events. A series of prodrugs have been evaluated in the *Salmonella typhimurium* TA98 tester strain and all possess anti-mutagenicity activity [154]. These cytotoxic and redox modulatory properties of the prodrugs relate to TrxR expression [155].

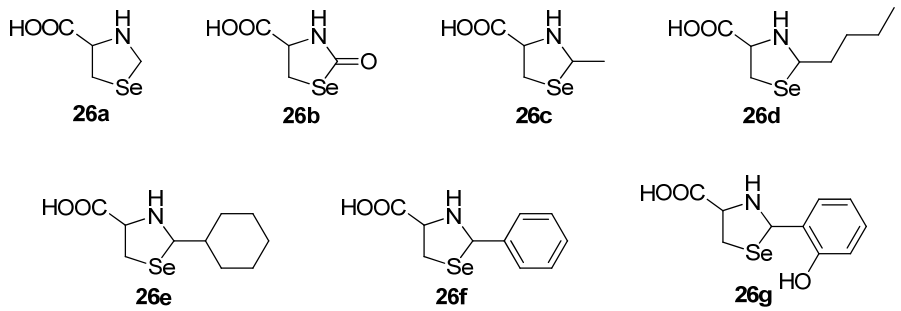
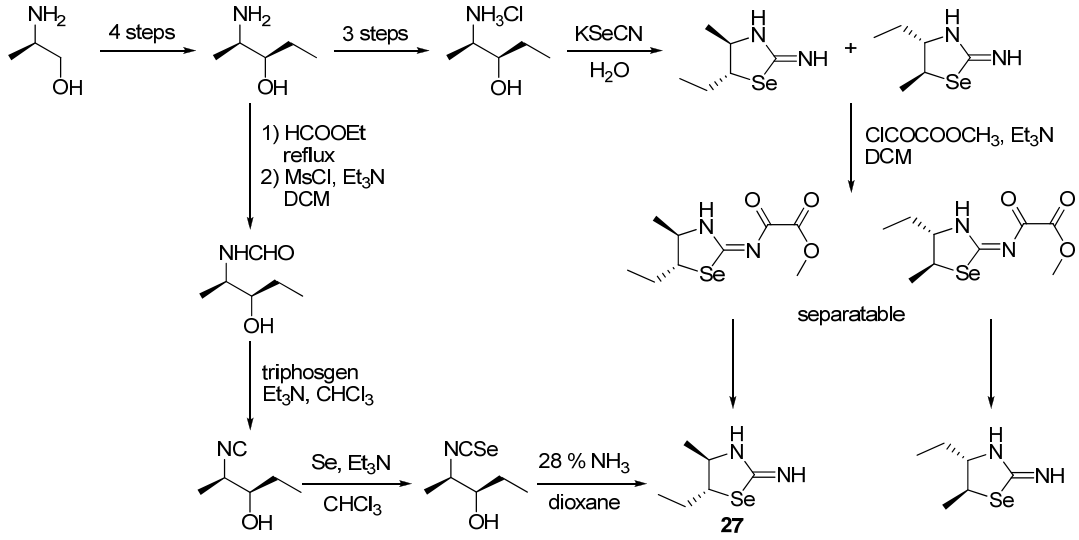


Fig. 7. Chemical structures of selenazolidine prodrugs.

5*R*-Ethyl-4*R*-methyl-2-iminoselenazolidine **27** was prepared by two synthetic methods, that is, through aziridine system and isoselenocyanate system (Scheme 12) [156,157]. This compound **27** showed strong inhibitory activity against iNOS and the best selectivity for iNOS. The *in vivo* study indicated that the **27**, given orally, strongly inhibited LPS-induced increase in plasma nitrite/nitrate levels in mice with the IC_{50} value of 0.30 mg/kg. In addition, the **27** indicated a good pharmacokinetic profile in rat with 73 % bioavailability.

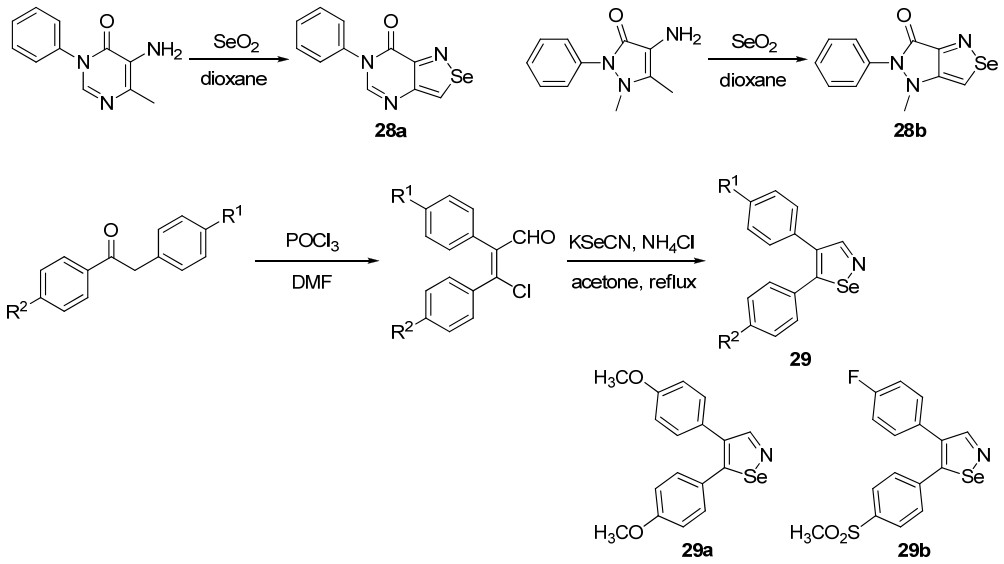


Scheme 12. Synthesis of 5*R*-Ethyl-4*R*-methyl-2-iminoselenazolidine.

Selenazole rings, first appeared in 1889 [158], and contain one Se atom, one N atom, and two double bonds. The selenazole moiety is present in many pharmacologically active substances such as selenazofurin and amselamine. Considerable interest in the synthesis and biological activity of selenazoles exits due to their potential for practical applications.

Isoselenazole (1,2-selenazole) is one of the selenazoles containing one N atom at 2-position. The oxidative reaction of 5-amino-6-methyl-3-phenyl-4(3*H*)-pyrimidone or 4-aminoantipyrine with selenium dioxide gave 6-phenyl-7(6*H*)-isoselenazolo[4,3-*d*]pyrimidone **28a** or 4,5-dihydro-4-methyl-6-oxo-5-phenyl-6*H*-pyrazolo[4,5-*c*]isoselenazole **28b**, respectively (Scheme 13) [159]. The compound **28a** markedly inhibited the growth of P388 mouse leukemia at dose of 100 μg/mouse/day × 10 without toxicity. The anti-tumor activity of **28b** was weaker than that of **28a**. The total lipid and phospholipid contents in the leukemia cells treated with **28a** were significantly decreased. The synthesis of DNA or RNA was depressed in the **28a**-treated leukemia cells [160]. Recently, cyclooxygenase/5-lipoxygenase (COX/5-LOX) inhibitors and hydroxyl radical scavengers of 4,5-diarylisoselenazoles have been reported [161]. The ketones reacted with phosphoryl chloride in Vilsmeier reaction conditions leading to the chloro-formylstilbenes. The 4,5-diarylisoselenazoles **29** were synthesized using potassium selenocyanate and ammonium chloride. After substitution of the chloride by selenocyanate, ammonia reacted with the formyl group of the imide, which finally

attacked selenocyanate releasing hydrogen cyanide. Among the compounds synthesized, **29a** exhibited the strong COX-2 inhibition (IC_{50} = 8 μM), and more potent with regard to the COX-1 inhibition (IC_{50} = 0.006 μM), however the 5-LOX inhibition is low. The most balanced compound in this series was compound **29b** including COX-1, COX-2, and 5-LOX inhibitory activities and weak hydroxyl radical scavenging potency.

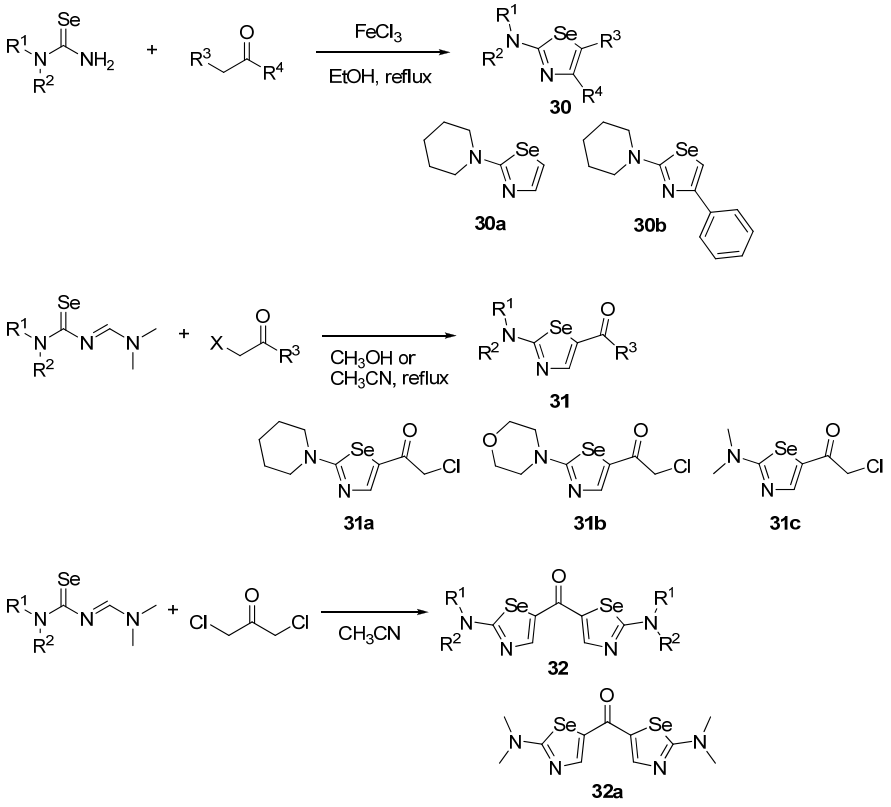


Scheme 13. Synthesis of bioactive isoselenazoles.

1,3-Selenazole, which contains N atom at 3-position and two double bonds, has been extensively studied in comparison with other Se-containing heterocycles because of its pharmaceutical applications [162-164]. 1,3-Selenazole is distinguished from 4,5-dihydro-1,3-selenazole (formerly called selenazoline) having only one double bond. The important starting materials for the 1,3-selenazole synthesis are selenoamides, selenoureas, selenazadienes, and isoselenocyanates [165-167]. Our group has reported the synthesis of a variety of 1,3-selenazoles using them. This part deals with the synthesis and biological activity of 1,3-selenazoles mainly based on our observations.

We investigated the superoxide anion scavenging effects of thirteen 2-dialkylamino-1,3-selenazoles **30** using a highly sensitive quantitative chemiluminescence method [168]. The 2-dialkylamino-1,3-selenazoles were prepared by the reaction of *N*,*N*-unsbstituted selenoureas with ketones in presence of ferric chloride [169]. At 166 μM, the 2-dialkylamino-1,3-selenazoles scavenged in the range of 14.4–96.7%. 2-Piperidino-1,3-selenazole **30a** and 4-phenyl-2-piperidino-1,3-selenazole **30b** exhibited the strongest superoxide anion scavenging activity among the the compounds tested. The IC_{50} values were 4.03 μM and 92.6 μM, respectively. Besides, the reaction of selenazadienes with α-haloketones gave 5-acyl-2-dialkylamino-1,3-selenazoles **31** (Scheme 14) [170]. Among them, three selenazoles, 5-chloroacetyl-2-piperidino-1,3-selenazole **31a** and 5-chloroacetyl-2-morpholino-1,3-selenazole **31b** strongly inhibited LPS-induced nitric oxide release from BV2 microglial cells [171]. These two compounds and 5-chloroacetyl-2-dimethylamino-1,3-selenazole **31c** induced the phosphorylation of

extracellular receptor kinase (ERK) [172]. Because the selenazole-induced phosphorylation of Akt and mitogen-activated protein (MAP) kinase cascades was responsible for suppression of apoptosis and facilitation of neuronal differentiation of PC12 cells, the three 5-acyl-2-dialkylamino-1,3-selenazoles are promising candidates as neuroprotective and/or neurotrophic agents for the treatment of various neurodegenerative neurological disorders. In addition, the 5-chloroacetyl-2-piperidino-1,3-selenazole **31a** is an inhibitor of melanin production in B16F10 cells by suppressing tyrosinase activity and expression of melanogenic enzymes [173]. We next investigated the reaction of selenazadienes with 1,3-dichloro-2-propane. Reactions produced the corresponding bis[2-dialkylamino-5-(1,3-selenazoyl)]ketones **32**. Bis[2-dimethylamino-5-(1,3-selenazoyl)]ketone **32a** exhibited the strong superoxide anion scavenging activity. The IC_{50} value of this compound was 37.1 μM [174].



Scheme 14. Synthesis of 2-dialkylamino-1,3-selenazoles.

5-Arylamino- and 6-arylthio-4,7-dioxobenzoselenazoles **33** were synthesized and tested for *in vitro* anti-fungal activity against *Candida* and *Aspergillus* species. The activities of compounds **33a**, **33b**, and **33c** were superior to those of 5-fluorocytosine as a standard agent against all tested fungi (*C. albicans*, *C. tropicalis*, *C. krusei*, *A. niger*, and *A. flavus*). The 5-Arylamino-4,7-dioxobenzoselenazoles **33a** and **33b** completely inhibited the growth of all fungal species tested at the MIC of 12.5 μg/ml [175]. Based on a homology-modeled structure of phospholipid transfer protein (PLTP) and characteristic structural features of cholesteryl ester transfer protein (CETP) inhibitors, a series of 2,4,5-trisubstituted selenazoles were synthesized. Biological evaluation revealed that

selenazoles **34a** and **34b** exhibited favorable PLTP activity, and their IC_{50} values were 8 μM and 10 μM, respectively [176].

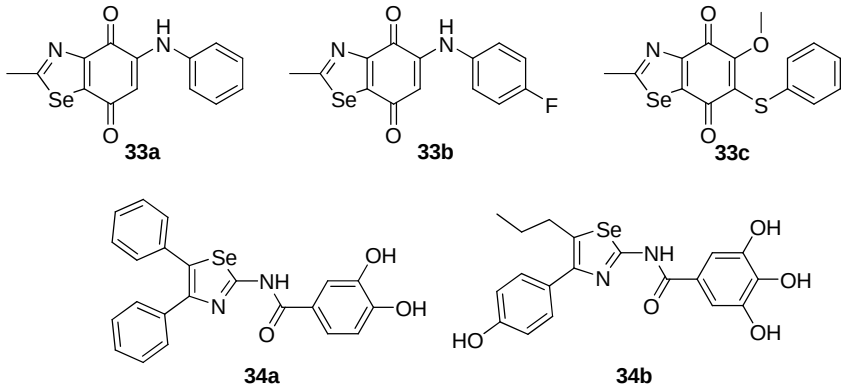
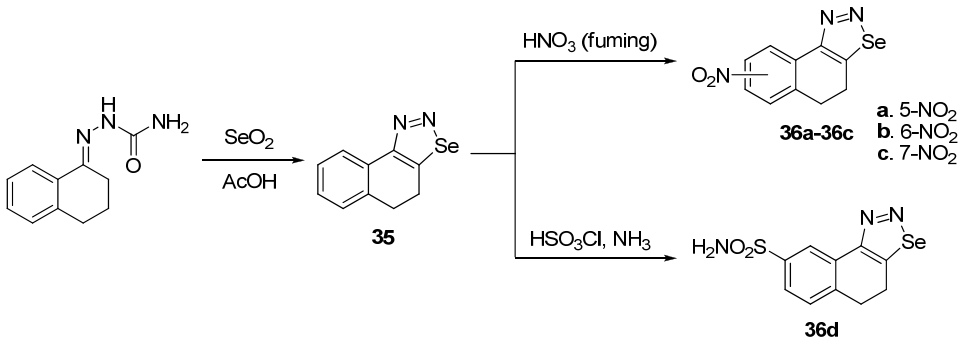


Fig. 8. Chemical structures of bioactive 1,3-selenazole derivatives.

Selenadiazoles are 5-membered cyclic compounds containing one Se atom, two N atoms, and two double bond. In the 1970s, the synthesis of selenadiazoles, by selenium dioxide oxidation of aldehyde or ketone semicarbazones having an α-methyl or methylene group, and their anti-bacterial and anti-fungal activities were reported by Lalezari and co-workers [177-180].

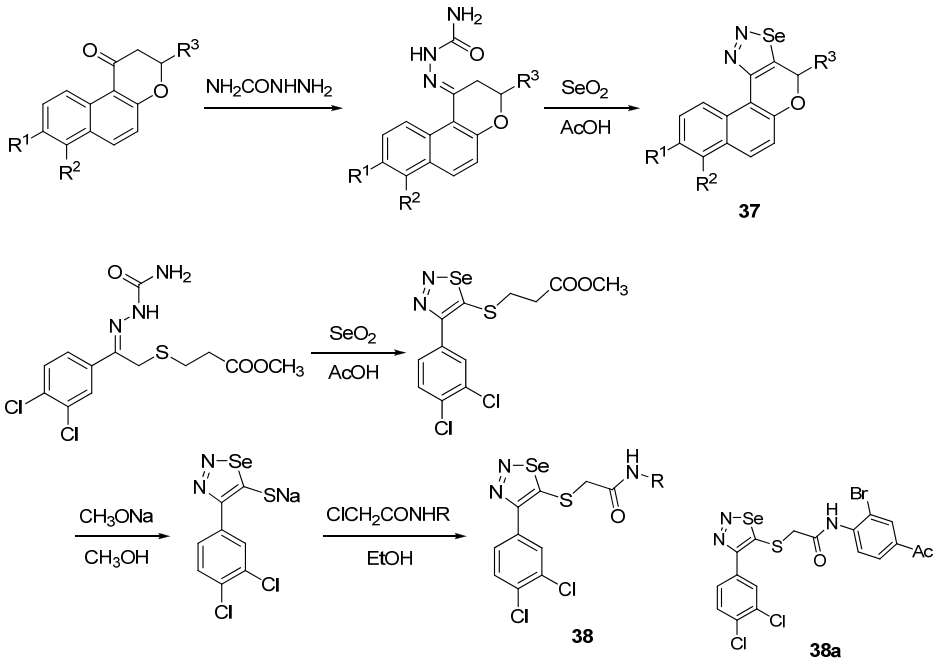
Several 4,5-dihydronaphtho[1,2-*d*][1,2,3]selenadiazoles were prepared and evaluated for their anti-fungal activities *in vitro* [181]. 4,5-Dihydronaphtho[1,2-*d*][1,2,3]selenadiazole **35** was synthesized by the reaction of selenium dioxide with the semicarbazone in acetic acid. Nitration of the selenadiazole **35** using fuming nitric acid produced 5-, 6-, and 7-nitro derivatives **36a-36c**. The reaction of the selenadiazole with chlorosulfonic acid followed by ammonia gave its 8-sulfamoyl derivative **36d** (Scheme 15). The 7-nitro derivative **36c** showed significant anti-fungal activity against *Cryptococcus neoformans* (MIC = 3.12 μg/ml).



Scheme 15. Synthesis of 4,5-dihydronaphtho[1,2-*d*][1,2,3]selenadiazoles.

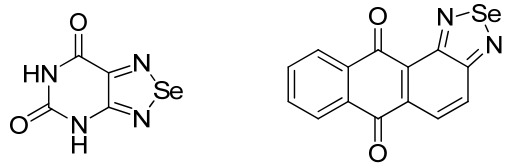
Tetracyclic-ortho-fused 4*H*-naphtho[1`,2`-5,6]pyrano[3,4-*d*](1,2,3)selenadiazoles were synthesized (Scheme 16) [182]. These molecules showed weak anti-bacterial activity against Gram-positive and Gram-negative bacteria. Based on bioisosteric principle, 1,2,3-selenadiazole thioacetanilides were designed and synthesized as new HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) [183]. These

1,2,3-selenadiazole derivatives were evaluated for their anti-HIV activity in MT-4 cells. The **38a** possessed potent activity against HIV-1 replication (IC_{50} = 2.45 μM), but this compound was not active against HIV-2 replication.



Scheme 16. Synthesis of 4*H*-naphtho[1`,2`-5,6]pyrano[3,4-d](1,2,3)selenadiazoles and 1,2,3-selenadiazole thioacetanilides.

1,2,5-Selenadiazoles are also interesting compounds as medicinal agents. In general, 1,2,5-selenadiazole rings are synthesized from the corresponding ortho-aromatic diamines by using an optimized microwave-associated solid state synthesis method (Fig. 9) [184]. 1,2,5-Selenadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **39** possessed broad spectrum of inhibition against various human cancer cells *via* the induction of apoptosis [185]. Anthrax[1,2-*c*][1,2,5]selenadiazolo-6,11-dione **40** induces time- and dose-dependent apoptotic cell death in MCF-7 human breast carcinoma cells [186].



39 **40**

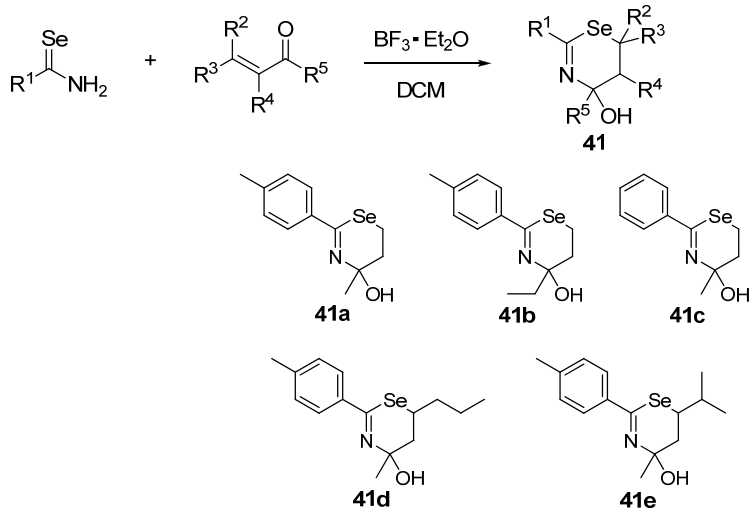
Fig. 9. Chemical structures of bioactive 1,2,5-selenadiazole derivatives.

7. Se-containing 6-membered rings

Biological investigations of Se-containing 6-membered rings have increased in recent years. In 1968, 2-chloro-1,3-benzoselenazin-4-one was prepared through cyclizing

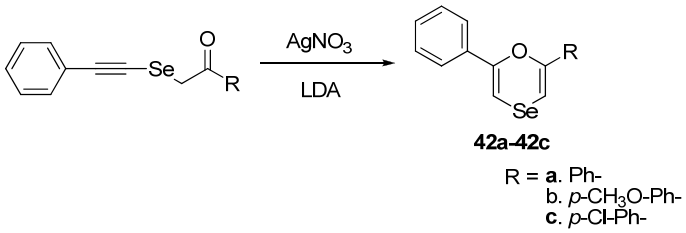
o-selenocyanatobenzoyl chloride using hydrogen chloride by the German chemist Simchen [187].

Our group was interested in the skeleton of 1,3-selenazine ring, and began investigations of these compounds. We adopted selenoamides as starting materials because the selenoamides contain the selenoamide-selenoimidate tautomerism and bear two reactive sites. The reaction of primary selenoamides with α,β-unsaturated ketones in the presence of $BF_3 \cdot Et_2O$ provided 5,6-dihydro-4*H*-1,3-selenazines **41** (Scheme 17) [188]. Among these compounds, 4-hydroxy-4-methyl-2-(4-tolyl)-5,6-dihydro-4*H*-1,3-selenazine **41a**, 4-ethyl-4-hydroxy-2-(4-tolyl)-5,6-dihydro-4*H*-1,3-selenazine **41b**, and 4-hydroxy-4-methyl-2-phenyl-5,6-dihydro-4*H*-1,3-selenazine **41c** exhibited strong inhibitory activity against both Gram-positive and Gram-negative bacteria [189]. The **41b** and 4-hydroxy-4-methyl-6-propyl-2-(4-tolyl)-5,6-dihydro-4*H*-1,3-selenazine **41d** showed the anti-proliferative effects against human HT-1080 fibrosarcoma cells [190]. These two selenazines **41b** and **41d** also showed strong growth inhibition of TMK-1 gastric cancer cells *via* the induction of apoptosis [191]. These results indicated that the **41b** and **41d** are potential candidates for further evaluation as anti-cancer agents. Furthermore, the **41b** and 4-hydroxy-6-isopropyl-4-methyl-2-(4-tolyl)-5,6-dihydro-4*H*-1,3-selenazine **41e** were potent and selective eukaryotic elongation factor-2 kinase (eEF-2K) inhibitors [192].



Scheme 17. Synthesis of 5,6-dihydro-4*H*-1,3-selenazines.

1,4-Oxaselenins are unique structural compounds. We have reported the preparation of three 1,4-oxaselenins **42a-42c** from 3-selena-4-pentyn-1-one by treatment of 2-bromoacetophenones with $AgNO_3$ and LDA (Scheme 18). 2-(4-Chlorophenyl)-6-phenyl-1,4-oxaselenin **42c** showed the inhibitory effect against the proliferation of human cancer cells and inducing effects on the early stage of apoptosis [193].



Scheme 18. Synthesis of 1,4-oxaselenins.

Selenomorphine derivatives were synthesized using the Mannich reaction and evaluated for their effects on the growth of *S. aureus* as studied by microcalorimetry (Fig. 10) [194,195]. Experimental results reveal that the sequence of anti-bacterial activity is **43a** > **43b**. The synthesis of selenium analogue **44** of bemoradan, which is a phosphodiesterase (PDE) inhibitor, was performed [196]. Unfortunately, selenium substitution in bemoradan lowered the activity of the bemoradan.

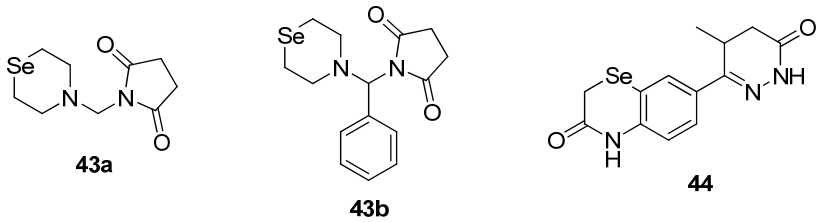
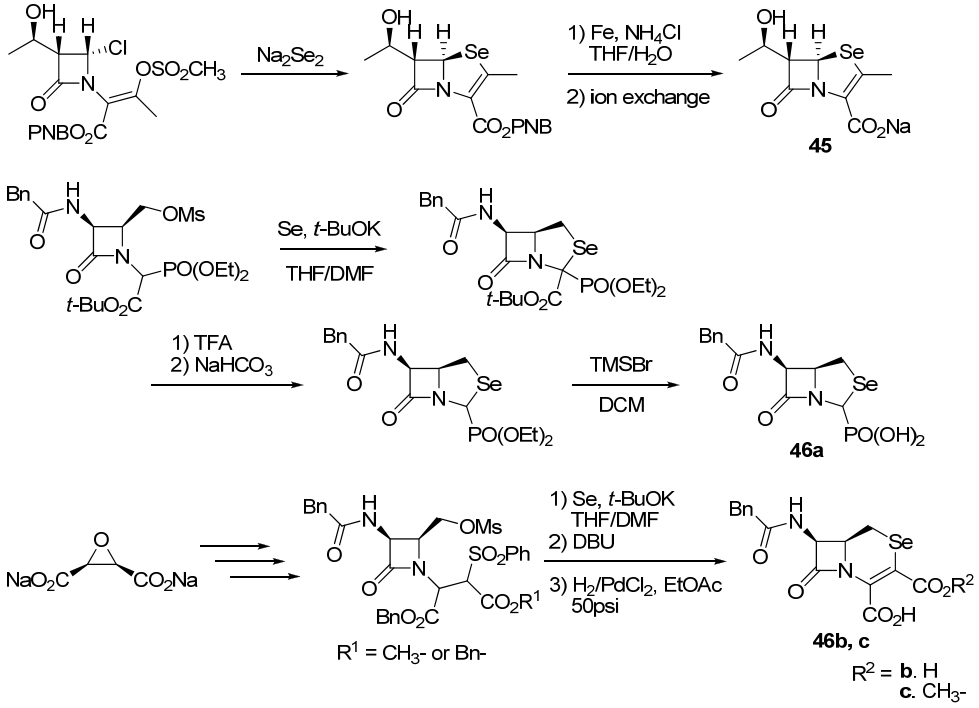


Fig. 10. Chemical structures of selenomorphine derivatives and selenium analogue of bemoradan.

8. Se-containing β-lactams

The discovery of the β-lactam antibiotics in the early 20th century represented a turning point in the struggle against pathogenic bacteria. These relatively inexpensive and highly efficient semi-synthetic products have been the mainstay of anti-infective chemotherapy for the past sixty years. The semi-synthetic penicillins and cephalosporins (amoxicillin, ampicillin, cephalexin, cefadroxil, cefazolin, and several others) correspond to 65 % of the ever rising worldwide production of antibiotics, exceeding 45,000 tons in 2000 [197]. The β-lactam ring (2-azetidinone) system was first synthesized *via* [2+2] cycloaddition in 1907 by the German chemist Staudinger [198]. Later several synthetic researchers have aimed at the skeletal modification of the naturally occurring β-lactams. The first synthesis of Se-containing β-lactams was performed in 1986 by Perrone and co-workers [199]. They synthesized the 2-selenapenem **45** by cyclization of chloro-3,4-azetidinone with sodium selenide and then deprotection of *p*-nitrobenzyl group. Although the result was a big progress for organoselenium chemistry, anti-bacterial activity of the 2-selenacephem decreased (about 4-fold) in comparison with the sulfur counterpart. The synthesis and anti-bacterial activity of the *cis*-configurated isodethiaselenapenam **46a** as well as the isodethiaselenacephems **46b** and **46c** were reported in 1994 [200]. The key step of this synthetic approach involved addition of Se to the corresponding carbanions followed by internal alkylation (Scheme 19). The β-lactams

46a-46d, and ampicillin, cloxacillin, and penicillin G were tested *in vitro* against five pathogenic bacteria. The **46a** and **46b** exhibited low anti-bacterial activity; however, the **46c** and **46d** exhibited pronounced anti-bacterial activity. The profound anti-bacterial effects of the **46c** and **46d** might indicate that the electronic activation of the β-lactam moiety by an electron-withdrawing group (ester group) plays an important role in biological activity of β-lactams (Table 5) [201].

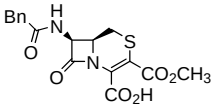


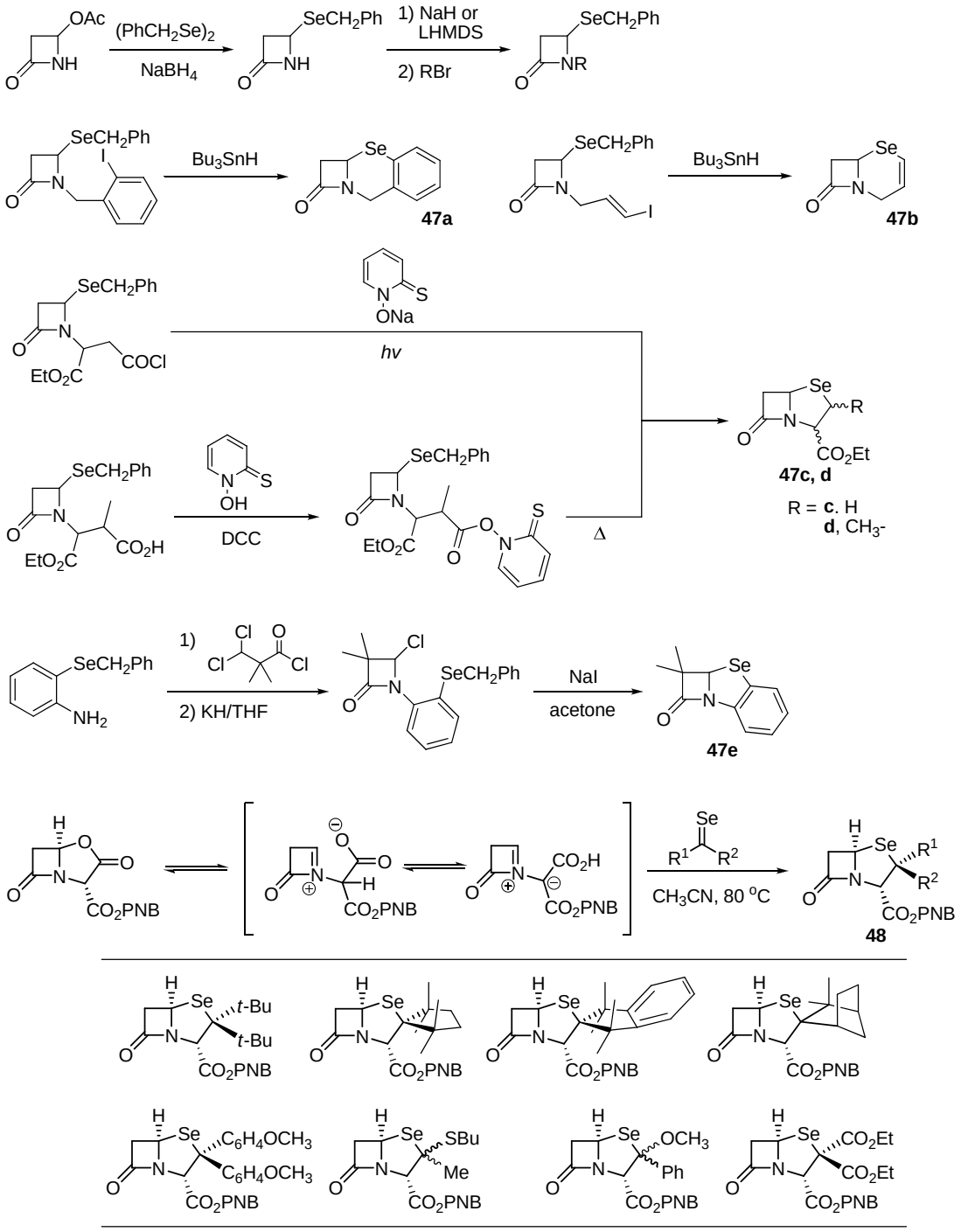
Scheme 19. Synthesis of 2-selenacephem, isodethiaselenapenam, and isodethiaselenacephems.

Table 5

Anti-bacterial activity of the 2-selenacephem, the isodethiaselenapenam, and isodethiaselenacephems [201]

	MIC (μg/ml)				
	S. Aureus FDA 209P	*E. coli* ATCC 39188	*S. typhi* O-901	*P. aeruginosa* 1101-75	*K. pneumoniae* NCTC 418
46a	65.40	n.a.	n.a.	98.50	n.a.
46b	1.20	15.35	38.65	39.45	25.60
46c	0.10	1.25	2.05	8.95	3.54
46d	0.07	0.65	1.50	13.00	2.15
Ampicillin	0.33	2.51	n.a.	n.a.	n.a.
Cloxacillin	0.18	1.70	n.a.	n.a.	n.a.
Penicillin G	0.40	2.30	n.a.	n.a.	n.a.

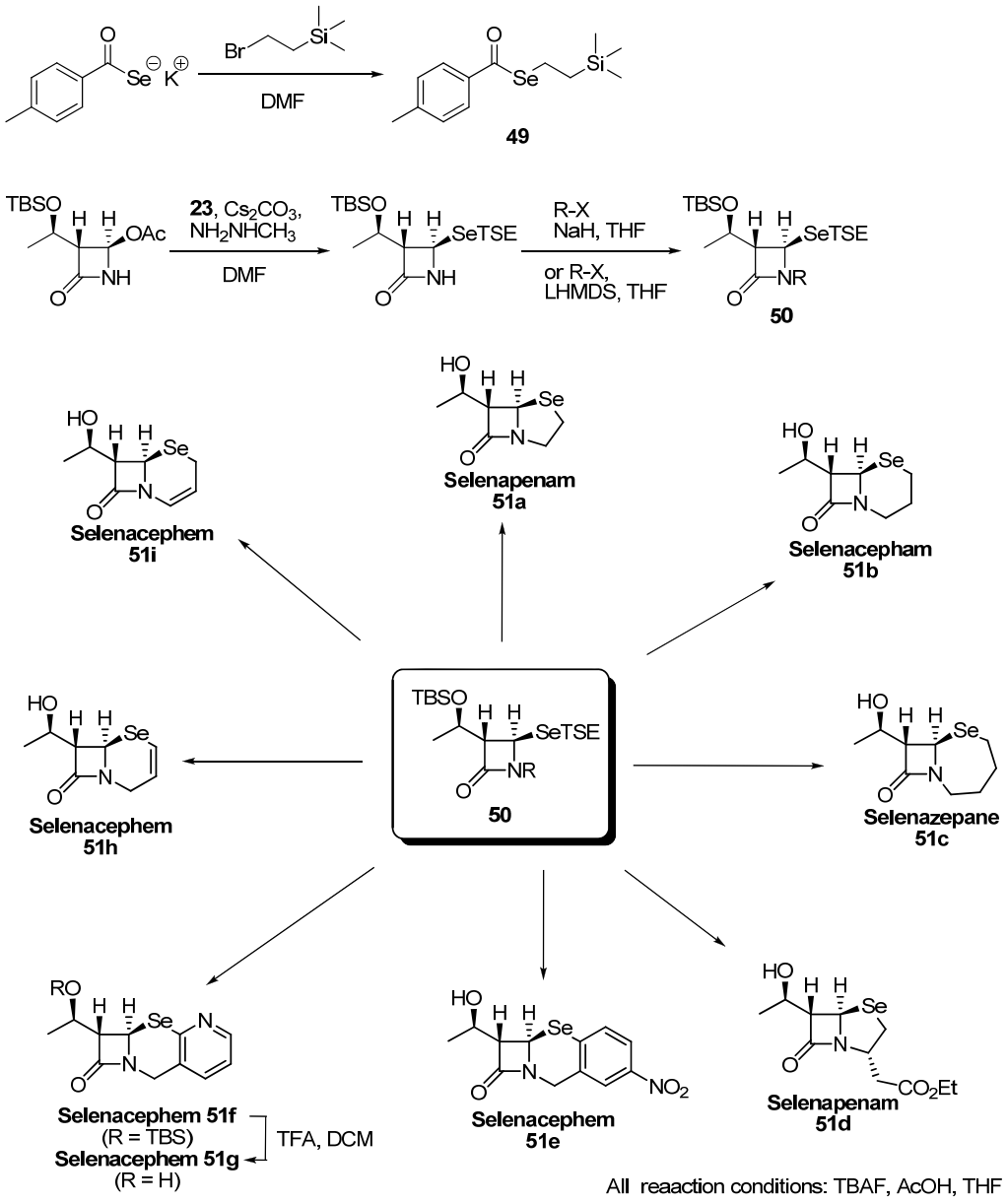




Scheme 20. Synthesis of several selenocephems and selenopenams.

The synthetic methodology of Se-containing β-lactams has been considered to be difficult. Nevertheless, several research groups endeavored to overcome the difficulty from the beginning of this century. Schiesser and co-workers have reported that selenopenams **47a** and **47b** and selenocephems **47c-47e** are conveniently prepared

through either intramolecular hemolytic or nucleophilic substitution chemistry involving the benzylseleno moiety (Scheme 20) [202]. In addition, the synthesis of selenapenams using azomethine ylide strategy has been performed (Scheme 20). The treatment of oxazolidinone with a variety of 2π dipolarophiles such as selenoketones, seleno- and selenothio-esters resulted in the formation of *C*(2) substituted selenapanams **48b** [203,204].

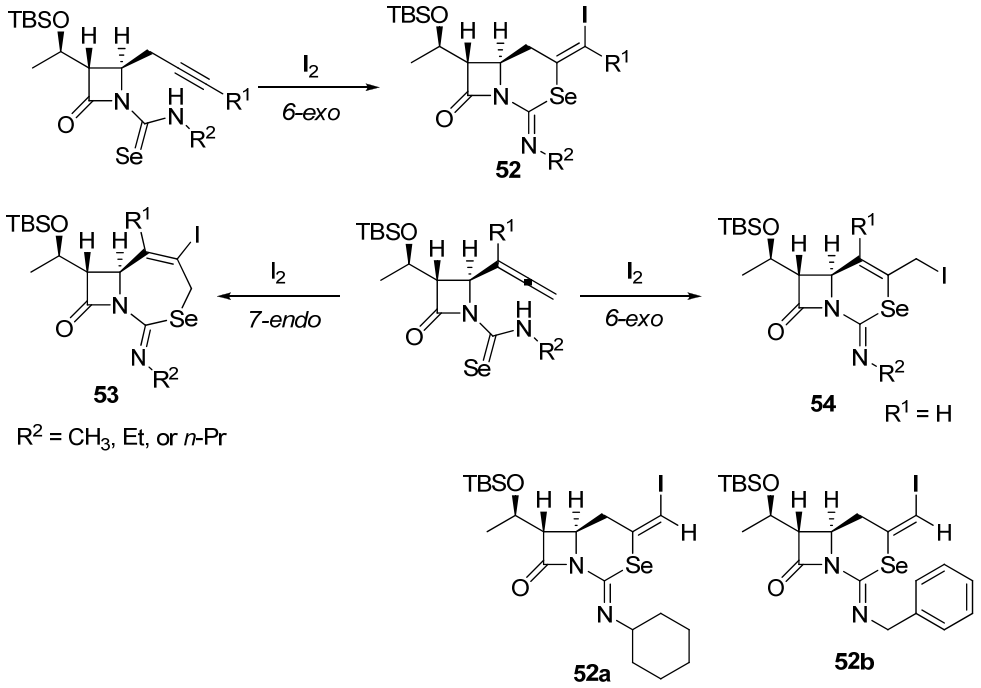


Scheme 21. Synthesis of various bicyclic Se-containing β-lactams using a TSE protection approach.

For the last five years, our group has reported several construction methods of the

bicyclic Se-containing β-lactam skeleton. The synthesis of selenapenams, selenacephems, and selenazepines using a 2-(trimethylsilyl)ethyl (TSE) protection approach was described [205]. In this investigation, we developed a new selenating reagent 2-(trimethylsilyl)ethyl *p*-methylselenobenzoate **49** on the basis of previous data [206-209]. This reagent is suitable for ring-closing synthesis because it has two latent reactive sites, that is, carbonyl carbon and tetramethylated silicon. We succeeded in producing novel selenapenams, selenacephems, and selenazepines **51a-51i** from TSE-selenyl intermediates **50** prepared by reaction of the new selenating reagent **49** and azetidinone (Scheme 21).

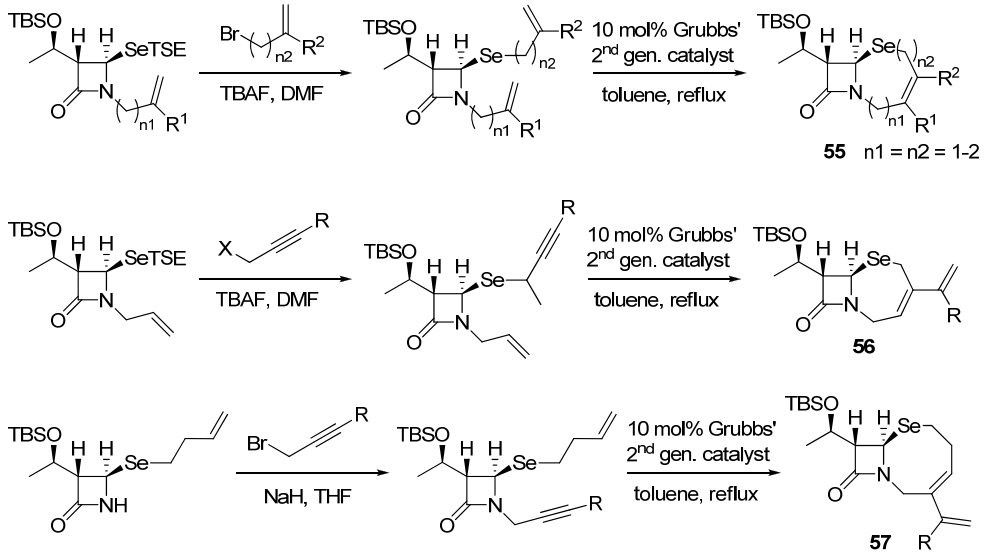
Later our efforts led to the synthesis of various kinds of Se-containing β-lactams *via* iodocyclization (Scheme 22) [210] and ring-closure metathesis (Scheme 23) [211,212]. Recently, a review about Se-containing bicyclic β-lactams was published by our group [213]. Furthermore, we evaluated possible chemopreventive properties of synthesized β-lactams in human prostate cancer LNCaP cells. Our observations suggested that *N*-cyclohexyl-3-selena-1-dethiacephem **52a** and *N*-benzyl 3-selena-1-dethiacephem **52b** could not only attenuate oxidative stress through Nrf2/ARE activation and direct ROS scavenging but also inhibit the cell growth. Thus, these compounds possessed the potential as pharmacological agents for chemoprevention of human prostate cancer [214].



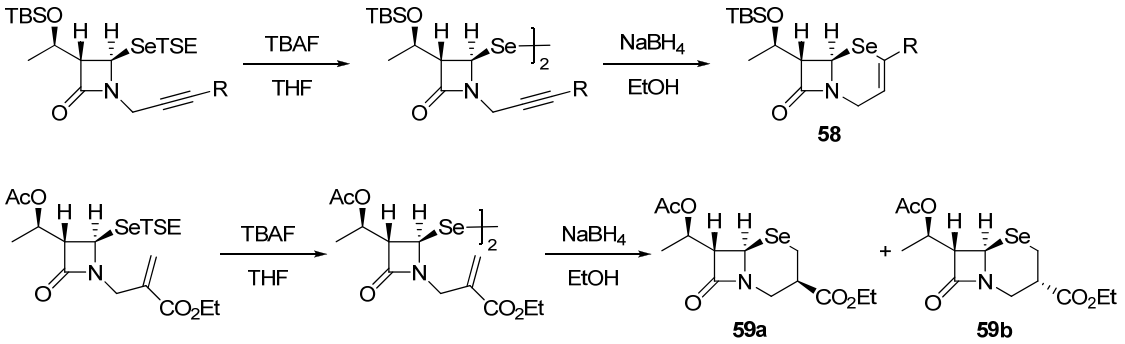
Scheme 22. Synthesis of 3-selena-1-dethiacephems and selenazepines *via* iodocyclization.

Very recently, we developed a pivotal approach for the synthesis of a variety of Se-containing β-lactams *via* cleavage of diselenide [215]. The treatment of the TSE-selenylazetidinone with tetra-*n*-butylammonium fluoride (TBAF) resulted in the formation of diselenide as the key intermediate for the subsequent reactions. The cleavage of the bisazetidinone diselenide by the action of sodium borohydride gave the

corresponding selenacephams **58** or selenacephems **59a** and **59b** (Scheme 24).



Scheme 23. Synthesis of various Se-containing bicyclic β-lactams *via* ring-closure metathesis.



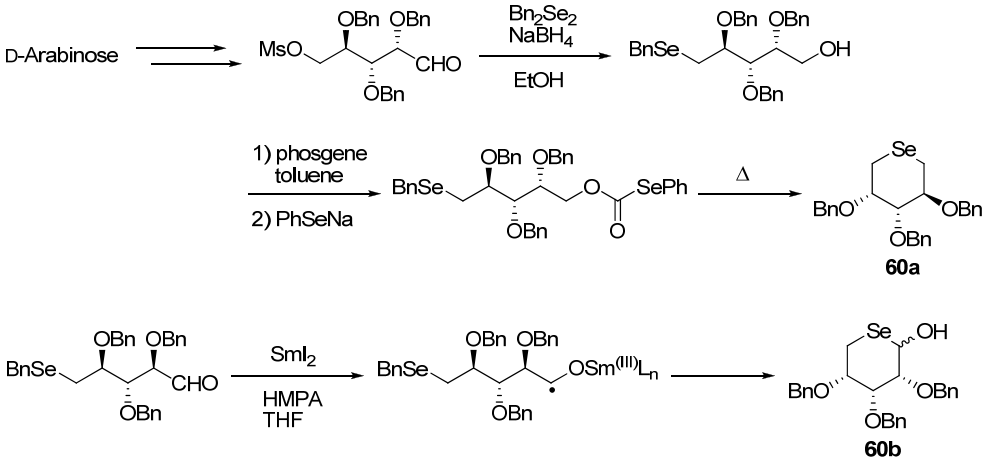
Scheme 24. Synthesis of selenacephams and selenacephems *via* cleavage of diselenide.

9. Se-containing biomolecule mimics

Libraries of Se-containing heterocycles based on biomolecules have gained importance in recent years. This section deals with Se-containing sugars, nucleosides, steroids, and vitamins.

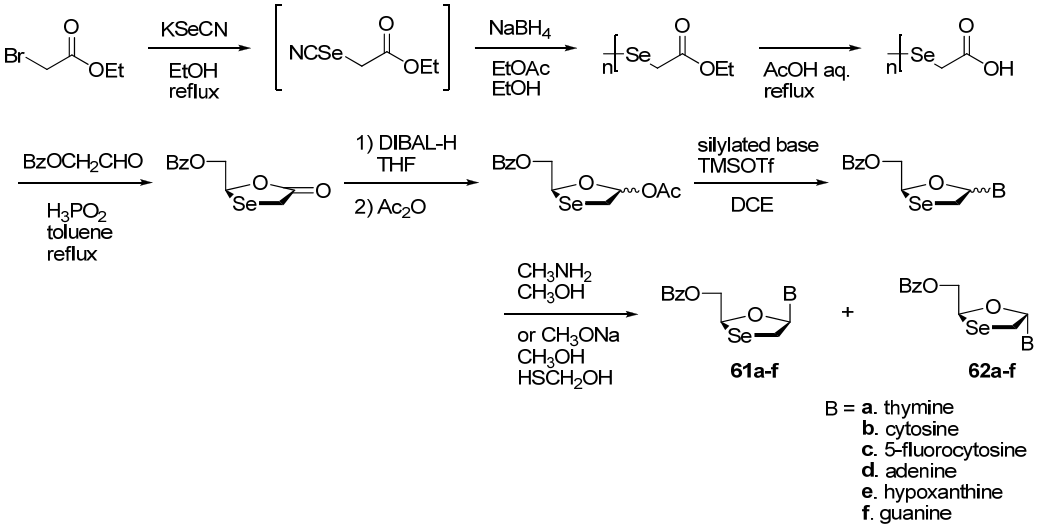
2,3,4-Tri-*O*-benzyl-1,5-dideoxy-5-seleno-D-pentopyranose sugars (**60a** etc.) were prepared by thermolysis of selenoformates in transformations which involved intramolecular nucleophilic attack of the benzylseleno moiety with concomitant loss of carbon dioxide and phenylselenoate. Further, treatment of 2,3,4-tri-*O*-benzyl-5-benzylseleno-5-deoxyribose with samarium (II) iodide afforded 2,3,4-tri-*O*-benzyl-5-deoxy-5-seleno-D-ribopyranose **60b** in a process most likely involving intramolecular homolytic substitution at the selenium atom in the selenosugar

(Scheme 25) [216].



Scheme 25. Synthesis of 5-selenopentopyranose sugars.

Various oxaselenolane nucleosides were synthesized from the key intermediate, (±)-2-benzoyloxymethyl-1,2-oxaselenolane 5-acetate (Scheme 26). Among the nucleosides synthesized, cytosine and 5-fluorocytosine β-analogues **61b** and **61c** exhibited potent anti-HIV (IC_{50} = 0.73–2.7 μM) and anti-HBV (IC_{50} = 1.2 μM) activities [217]. 2`,3`-Dideoxy-4`-selenonucleosides **63a-63c** and **64a-64c** were synthesized from a chiral template, D-glutamic acid using stereoselective ring-closure reaction of the dimesylate with selenium anion and Pummerer type condensation of the selenoxide with nucleobases as key steps (Fig. 11) [218]. Crystallographic analysis indicated that these 4`-selenonucleosides adopted the same C2`-*endo*/C3`-*exo* (South) conformation as anti-HIV active dideoxynucleosides, but did not show anti-HIV activity.



Scheme 26. Synthesis of oxaselenolane nucleosides.

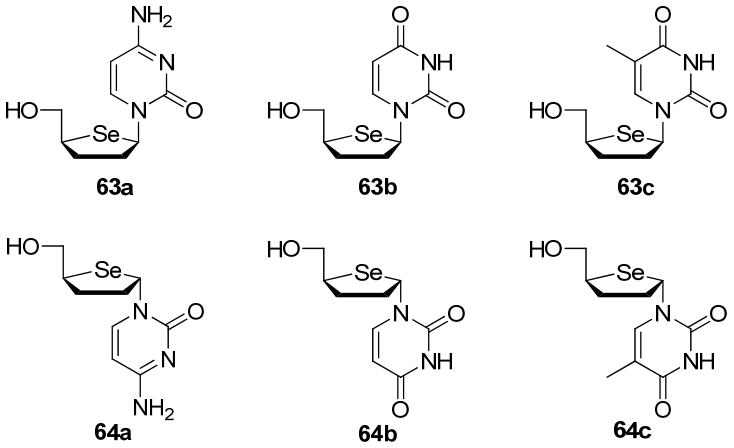
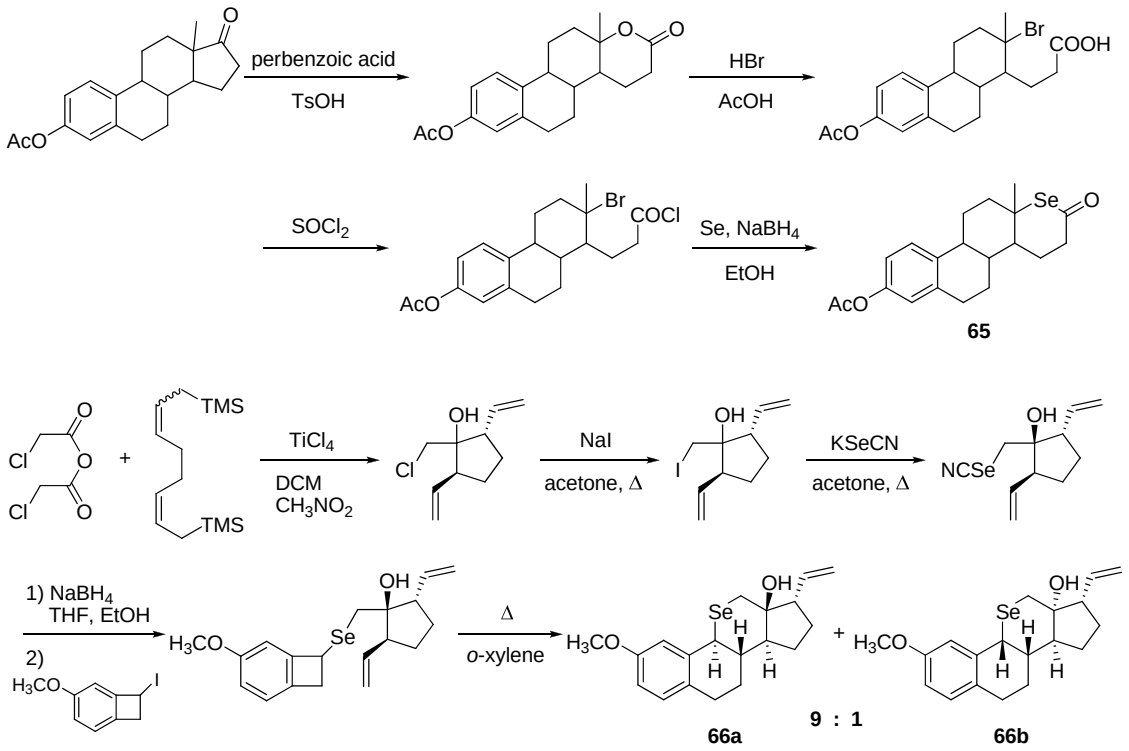


Fig. **11**. Chemical structures of designed 2`,3`-dideoxy-4`-selenonucleosides as potential antiviral agents.

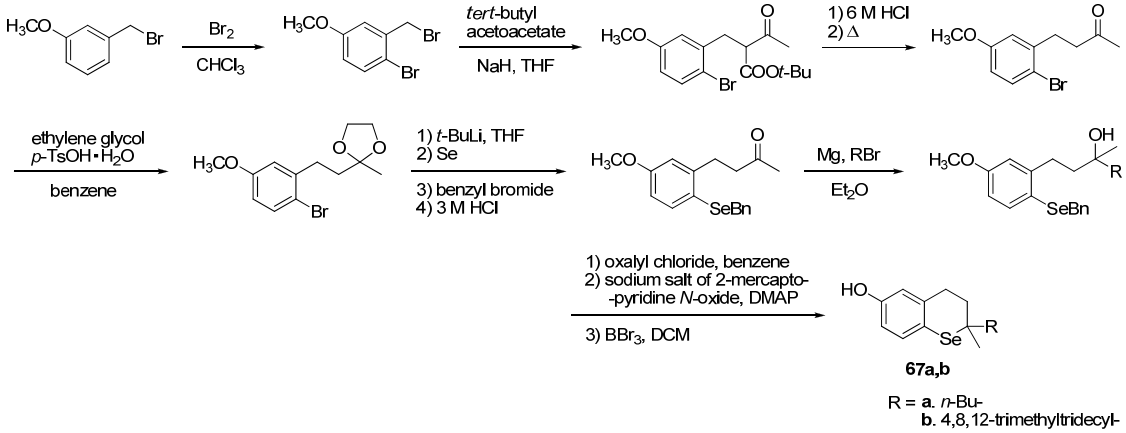
A successful approach in the synthesis of 3β-acetoxy-17*a*-selena-D-homo-1,3,5(10)-estratrien-17 one **65** was achieved from 3β-acetoxy-1,3,5(10)-estratrien-17 one [219]. In addition, the total synthesis of 11-selenasteroids **66a** and **66b** was achieved *via* an intramolecular Dies-Alder cycloaddition of *o*-quinodimethanes as the key step (Scheme 27) [220].



Scheme 27. Synthesis of selenasteroids.

Examples of intramolecular hemolytic substitution of tertiary radicals at selenium by

employing the Barton/Crich protocol for the selenium analogues **67a** and **67b** of vitamin E have been reported (Scheme 28) [221].



Scheme 28. Synthesis of selenium analogues **67a** and **67b** of vitamin E.

10. Conclusion

In conclusion, this review provides advances in the synthesis of selenium-containing heterocycles and their biological significance. This review surely will be of considerable potential in the designing of the biologically important selenium-containing heterocycles and for new structure-activity relationship studies.

.

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