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REVIEW

Synthetic Organo-Selenium Compounds in Medicinal Domain

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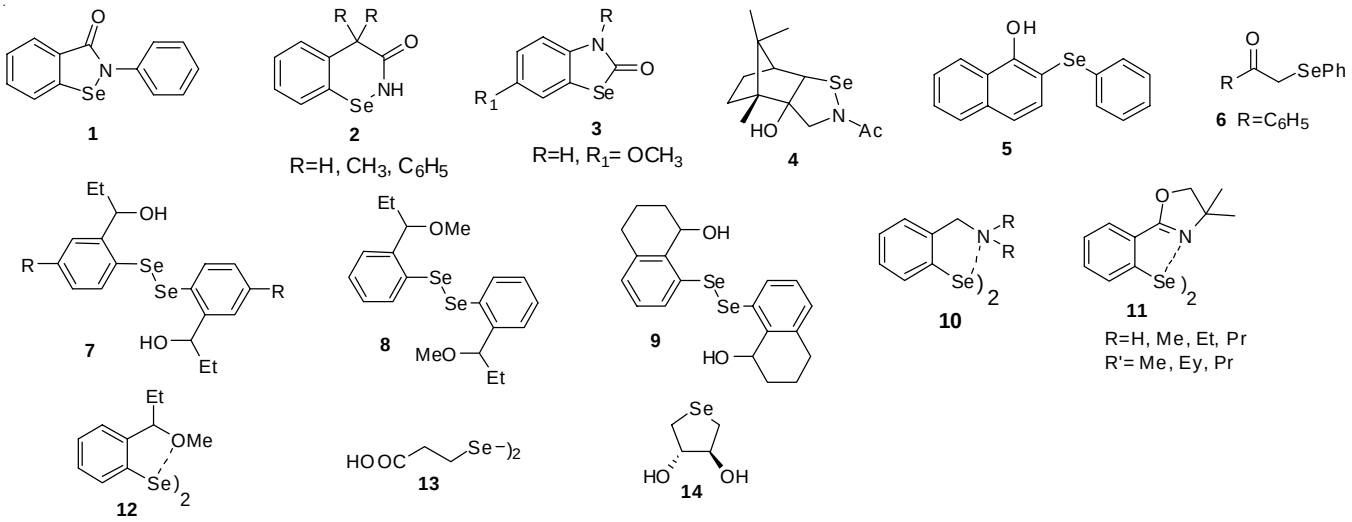
Organoselenium chemistry has emerged as an outstanding area in recent years due to its essential role in synthesis of a large number of biologically active compounds and important therapeutic products. The design and synthesis of organoselenium compounds with improved biological activity continues to be an active area of research. This minireview discusses the different medicinal applications of a plethora of synthetic organoselenium compounds from last two and a half decade. This mini review is aimed to be handy reference for synthetic chemists in designing and synthesizing novel organoselenium compounds of therapeutic significance.

Keywords: Organo-selenium compounds, Medicinal applications, Ebselen, Glutathione peroxidase, Cytoxicity.

INTRODUCTION

Schwarz and Foltz[1] reported selenium as a micronutrient for bacteria, mammals and birds. Only after 1970, when the formation of alkenes by decomposition of selenoxides was found to be a versatile process, proceeding under very mild conditions, explosive growth in the use of organoselenium chemistry occurred[2]. Over the last three decades, the synthesis of selenium compounds has been a center of attention among the synthetic chemists in view of their distinctive biological properties. Selenium compounds have been found to be glutathione peroxidase mimics (GPx)[3], thioredoxin reductase inhibitors[4], antioxidants[5], antitumor[6], antimicrobial[7], antiviral[8] and antihypertensive agents[9]. In eukaryotes, besides glutathione peroxidase iodothyronine, deiodinases, thioredoxin reductases[10] sele-nophosphate synthetase represent important classes of selenoenzymes. Several organoselenium compounds have been shown to prevent lung, mammary, tongue and colon cancers caused by polycyclic aromatic hydrocarbons[11,12]. Recent developments in selenium chemistry have been mainly in the area of selenocarbohydrate, selenopeptide and selenoamino acids with the aim of their use in enzymology, bioorganic and biomimetic chemistry[13]. In addition to potential biological applications, organoselenium compounds are also important in organic synthesis, electronic industry[14], as organic conductors[15], various metal organic chemical vapor deposition processes for the formation of semiconducting thin films[16], and materials, ligand chemistry and as sensitizers in photodynamic therapy[17]. All mammalian selenoproteins contain selenium in the form of the amino acid selenocysteine[18]. Reports suggest that inorganic selenium is incorporated in proteins by selenophosphate synthesis from selenide and ATP by a selenophosphate synthetase followed by incorporation of selenium atom into selenocysteine synthesized from seryl tRNA (*Sec*)[19,20]. Past two decades have witnessed a remarkable growth in the field of synthetic organoselenium chemistry, leading to the synthesis of a large number of biological compounds[21]. Recently, Rizvi *et al.*[22,23] reported the *in vitro* apoptotic potential and cytotoxicity of symmetric aromatic selenides. In this review, we compile an account of medicinal application of synthetic organo-selenium compounds.

Biological activity of selenium compounds: Enzymes like glutathione peroxidase (GPx) contain selenium as a component of the active site[24]. The glutathione peroxidase catalyzes the reduction of a variety of hydroperoxides (ROOH and H_2O_2) using glutathione as a reductant, thereby protecting mammalian cells from oxidative damage[25]. Several simple synthetic organoselenium compounds with glutathione peroxidase-like activity have been prepared in efforts to find mimics of glutathione peroxidase[26]. Ebselen (**1**) was the first synthetic compound suggested for hydroperoxide-inactivating therapy in the presence of glutathione[27]. In comparison to the reaction catalyzed by the enzyme, which contains binding sites conferring specificity for glutathione, ebselen and other organoselenium compounds can utilize a variety of thiols[28,29], in addition to glutathione, as a substrate. Based on the glutathione peroxidase



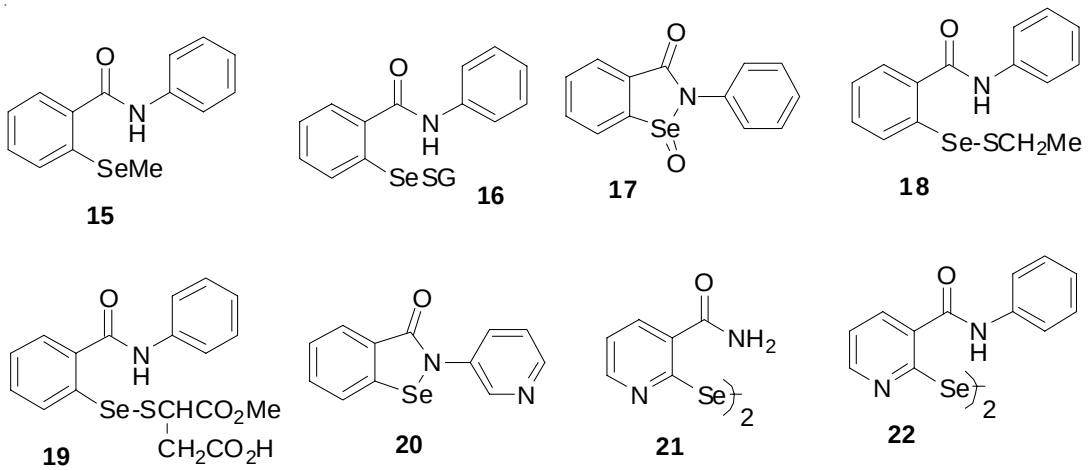
Scheme-I: Synthetic ebselen mimic organoselenium compounds

like activity of ebselen, several synthetic organoselenium compounds, such as benzoselenazinones (**2**), benzoselenazolinones (**3**), camphor-derived selenenamide (**4**), 2-phenylselenenyl-naphthol (**5**), R-(phenyl-seleny)-ketones (**6**) (**Scheme-I**) and oxygen-containing diselenides **7-9**, **10**, **11**, **12**, **13** and **14** have been synthesized in efforts to imitate ebselen activity.

Antioxidant activity: Selenoproteins such as glutathione peroxidase[30] or selenoprotein P have been reported to reduce peroxynitrite (PN) thereby, suggesting that ebselen and other organoselenium compounds can also serve to protect against peroxynitrite. Compound **15** for long time thought to be an inert metabolite of ebselen, reacts with peroxynitrite much faster than with H_2O_2[31]. Moreover, ebselen and related derivatives have also been shown to protect against lipid peroxidation induced by transition metals, *e.g.* iron/ADP-induced lipid peroxidation in microsomes and by methyl linoleate[32]. Compound **16**, **17** and **18-20** exhibit protective activities comparable to ebselen. Also, nicotinoyl based organoselenium compounds *i.e.*, **21** and **22** have shown remarkable activities as glutathione peroxidase mimic and free radical scavenger[33] (**Scheme-II**).

Enzyme inhibitors: Organoselenium compounds act as enzyme inhibitors of a variety of enzymes such as inosine monophosphate dehydrogenase (IMPDH), lipoxygenases (LOX), nitric oxide synthase (NOS), thymidylate synthase (TMS), tyrosine kinase (TK), uridine phosphorylase (UrdPase) and iodothyronine deiodinase (ID). In addition to these enzymes, some other enzymes such as NADPH oxidase, protein kinase C (PKC), glutathione-*S*-transferase (GST), NADPH-cytochrome reductase and papain are inhibited by ebselen and related derivatives.

Ebselen and other related organoselenium compounds have been reported to be inhibitors of constitutive endothelial NOS (ecNOS). The inhibition of nitric oxide (NO) formation by ebselen was first observed on the cellular level in experiments with rat Kupffer cells[34]. The carboxylated analogue of ebselen (**23**) was found to be more potent and selective than ebselen in the inhibition of ecNOS[35]. Similarly **24** bearing a polar substituent was less active, suggesting that the transport through cell membranes plays an important role in the biological action of the NOS inhibitors. The activity of IMPDH increases significantly in proliferating cells and its inhibitors are expected to be promising antitumor and immunosuppressive agents[36]. Besides IMPDH inhibitors are considered as potentiators of the anti-HIV activity of retroviral drugs such as 2',3'-dideoxyinosine (ddI). Both tiazofurin (**25**) and selenazofurin (**26**) have pronounced antitumor activity in animals and broad spectrum antiviral as well as maturation-inducing

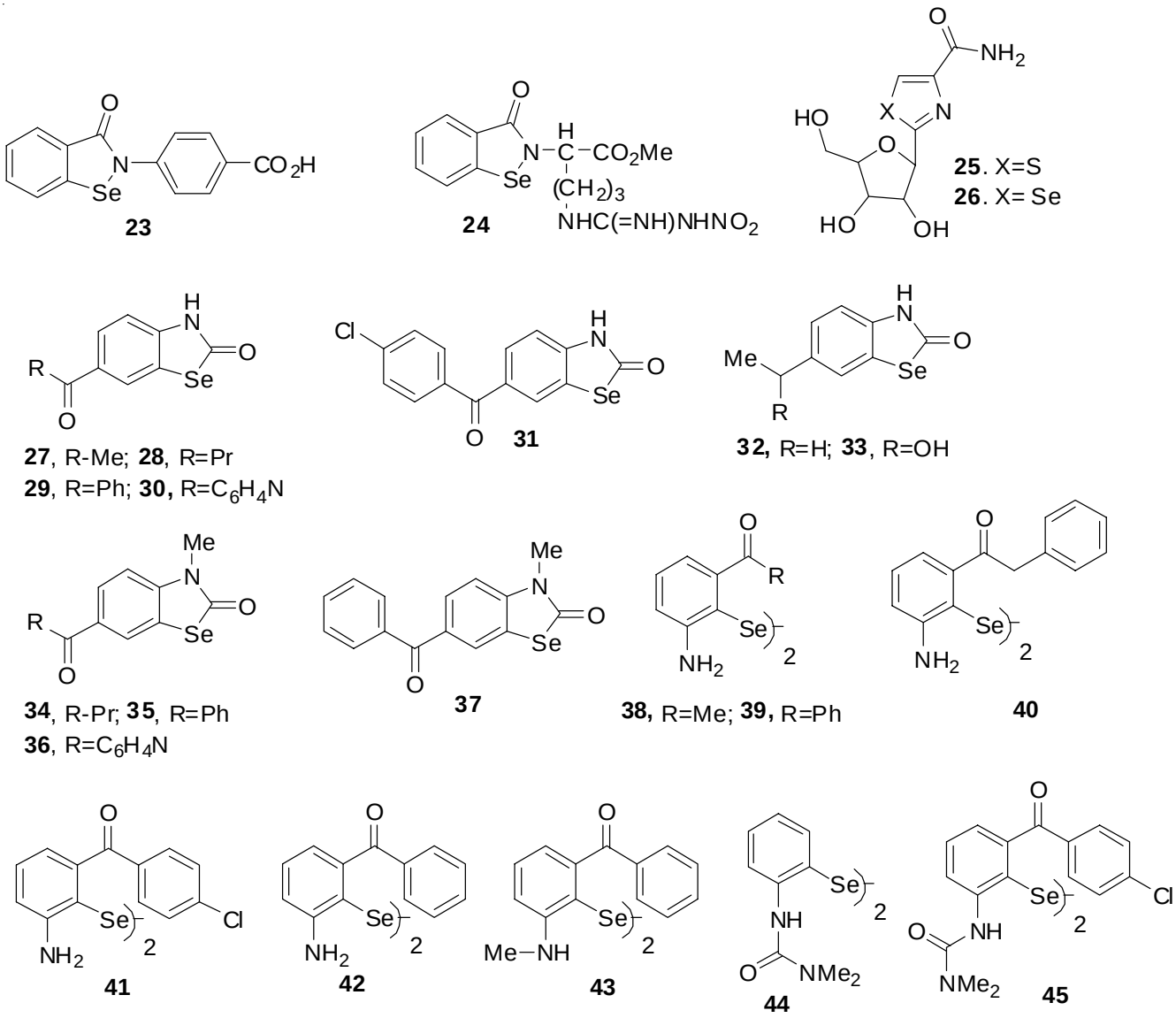


Scheme-II: Synthetic organoselenium derivatives tested as peroxynitrite antioxidants

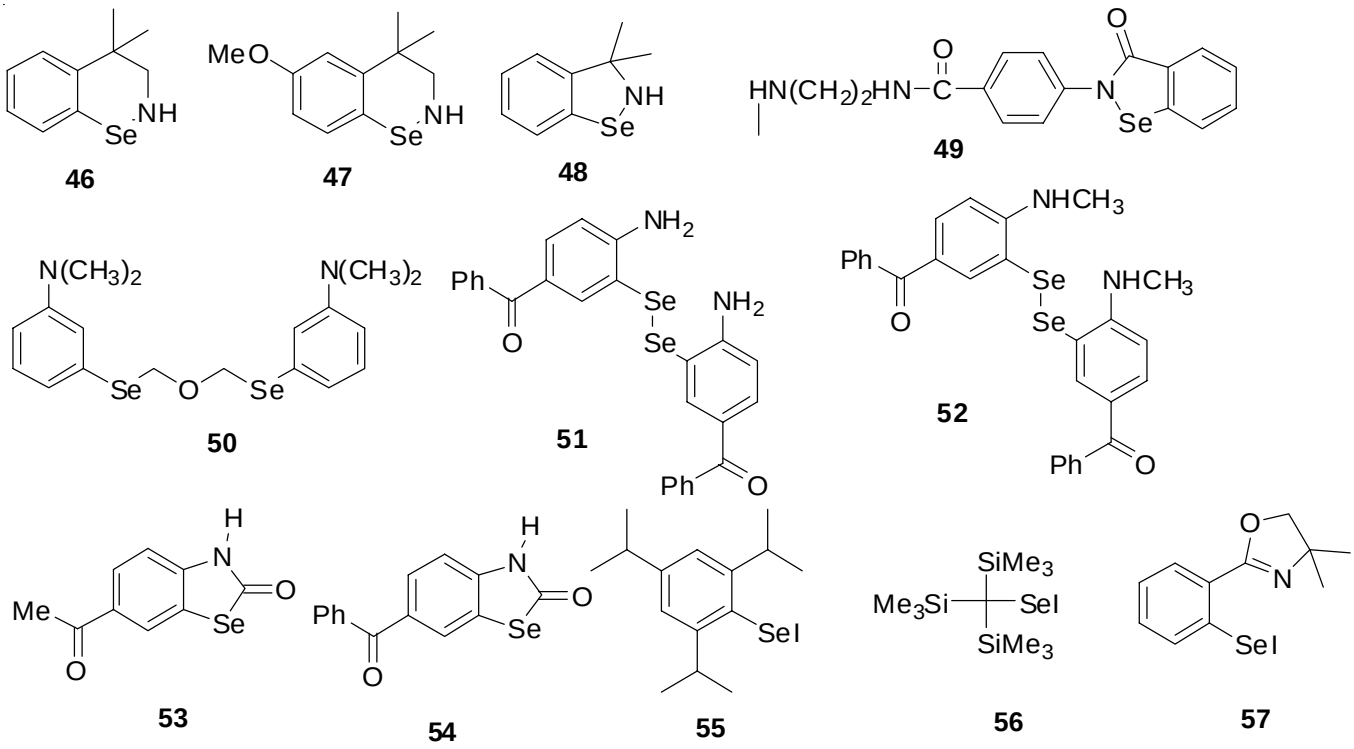
activities[37]. Selenazofurin is found to be 5-10 times more potent than tiazofurin *in vitro* antitumor screens[38] possibly due to the inhibition of IMPDH[39]. Selenazofurin has also been reported to be a potent inhibitor of phlebovirus infections, as this compound suppresses liver virus titers when administrated orally[40]. Some selenazoles are being studied as potential anti-inflammatory agents as they tend to be dual inhibitors of both cycloxygenase (COX) and 5-LOX. The valuable effects of ebselen have been accredited to the inhibition of the enzyme 5-LOX, thereby preventing production of pro-inflammatory cysteinyl leukotrienes[41]. Benzoselenazolinones **27-37** and the corresponding diselenides **38-45** have been reported to dramatically decrease the formation of leukotriene LTB4. Diselenides (**39-42**, **44** and **45**) also showed higher inhibitory properties for the formation of leukotrienes **Scheme-III**.

Anti-inflammatory activity: Though anti-inflammatory action of ebselen is thought to originate from its peroxidase activity however, this may not be the only mode of action of ebselen. Studies have shown that ebselen affects intracellular calcium homeostasis by inhibiting inositol-3-phosphate (IP3)-induced calcium release and also interferes with granulocyte oxidative burst by dual inhibition of NADPH oxidase and protein kinase C[42] Benzoselenazines (**46,47**) and benzoselenazole (**48**) derivatives, have been reported to prevent TNF-R and neutrophil-induced endothelial alterations. Compound **46** shows potent inhibition of TNF-α induced endothelial alteration and has been actually in clinical development as drug candidate for the treatment of ulcerative colitis[43].

Ebselen oxidation resistance of HOCl, suggests that ebselen might prove more useful as an anti-inflammatory agent than glutathione peroxidase enzyme[44]. Lower water solubility of ebselen can be a limitation attaching ebselen moiety to β-cyclodextrins (**49**) display excellent solubility and enhanced activity[45] *bis*-4(dimethylamino-phenylselenomethyl) ether (**50**) was found to be most potent inhibitor of formalin-induced paw edema in rats. Benzoselenazoline derivatives (compound **51-54 Scheme-IV**) are reported as potential COX and 5-LOX inhibitors. Compound **53** was found selective for the 5-LOX pathway and **52** a selective for the COX pathway, whereas **51** and **54** are found to be active for both. Interestingly, the antinociceptive and anti-inflammatory potency of diphenyl diselenide was also found higher than that of ebselen[46].



Scheme-III: Benzoselenazolines and their diselenide derivatives as enzyme inhibitors



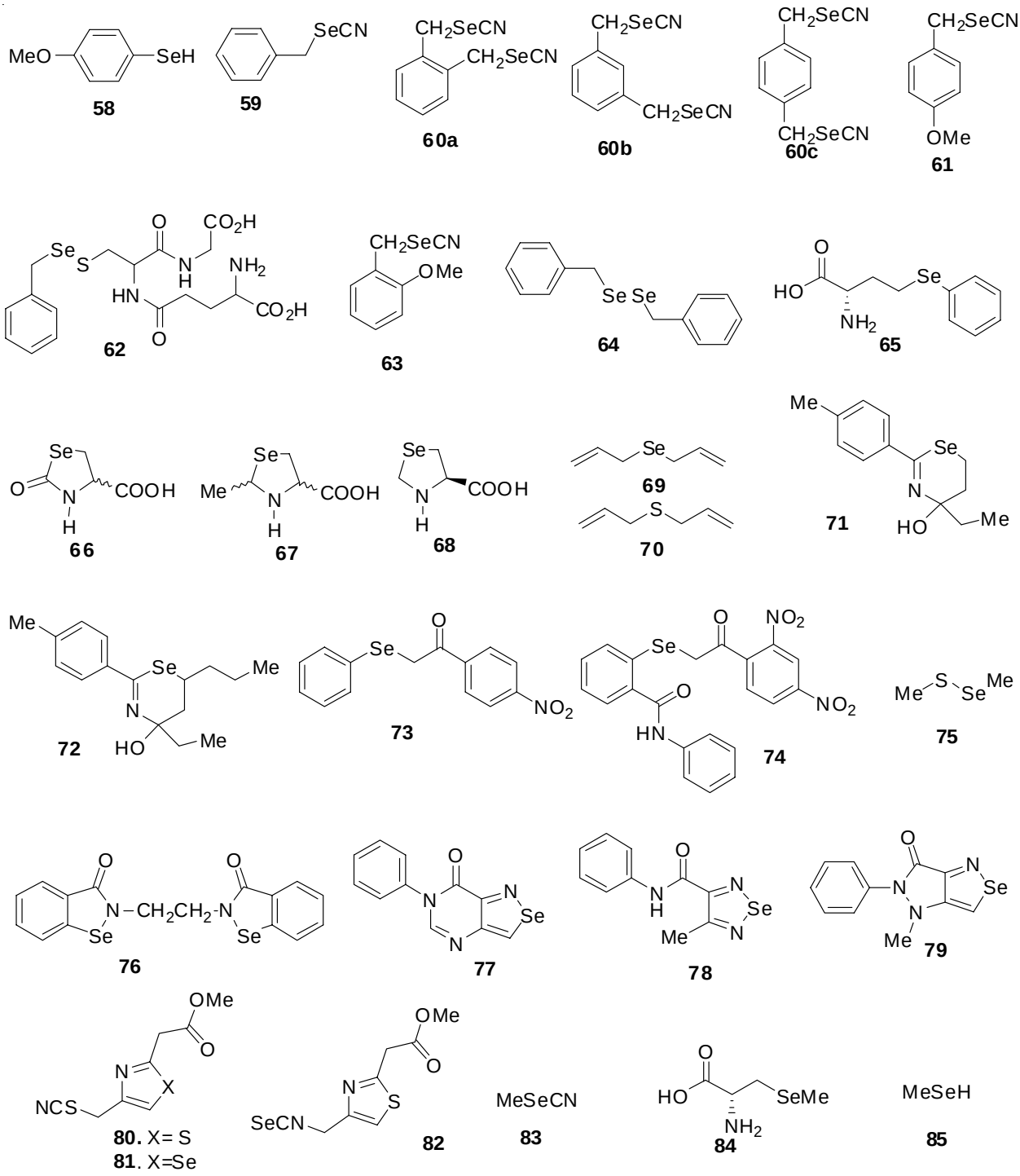
Scheme-IV: Synthetic anti-inflammatory organoselenium compounds

Chemopreventive activity: Shamberger and Frost[47] in 1960's proposed that selenium may have a possible protective effect against human cancer. *p*-Methoxybenzeneselenol (**58**), was the first organoselenium compounds used as a chemopreventive agent[48]. But it was soon replaced by benzylselenocyanate (**59**), which has been reported to inhibit the development of colon tumor and mammary tumors during the initiation phase of carcinogenesis in rats[49]. Further studies suggested that benzylselenocyanate changes expression of cellular proteins, which regulate transcription and replication of DNA sequences[50]. Compound **59** was also found to be an inhibitor of DNA cytosine methyltransferase from human colon carcinoma[51]. Besides, **59** inhibit PKC and PKA activities in cultures of primary human fibroblast[52]. 1,4-Phenylene*bis*-(methylene) selenocyanate (**60**) synthesized in an attempt to enhance the tumor inhibiting effects of **59**, resulted in enhanced potency and reduced toxicity[53]. Compound **60b** inhibits AOM-induced carcinogenesis by suppressing tyrosine protein kinase (TPK) and protein kinase C (PKC) activities and by up-regulating diacylglycerol kinase (DGK) activity. *para*-Phenylene-*bis*(methylene)selenocyanate (**60c**) was found efficient in experimental models for carcinogenesis at both initiation and post-initiation stages in colon[54], mammary glands, lung/liver[55], intestine and oral tissues[56]. Towards developing less toxic but effective chemopreventive agents, Kawamor[57], proposed benzylselenocyanateglutathione conjugate **62**, an active metabolite mediating the chemopreventive activity of benzylselenocyanate, as an inhibitor of azoxymethane-induced colon carcinogenesis. By the use of the same model of colon cancer, it was shown that **61** and **63** too have chemopreventive activity. Selenazolidines (**66-68**) **Scheme-V**, showed promising results as prodrugs of selenocysteine for cancer chemoprevention[58]. Diallyl selenide **69** was 300 times more active than diallyl sulfide **70** in inhibiting mammary cancer in rats[59]. 1,3-Selenazine derivatives, **71** and **72** were shown to inhibit human gastric adenocarcinoma cells by the induction of apoptosis[60]. Inhibitory capacity of naturally occurring selenium containing amino acids such as methylseleno-cysteine **84** and seleno-cysteine were tested against seven of the most important human P450s and benzylselenocysteine **65** was found to be the most potent inhibitor[61]. Lu and collaborators[62] reported that methylselenocyanate (**83**) and methylselenocysteine (**84**), which are metabolized predominantly to methyl-selenol (**85**), induced growth inhibition without DNA single-strand breakage.

Shi and co-workers[63] demonstrated that 1,2-[*bis*(1,2-benzisoselenazole-3(2*H*)-ketone]ethane (**76**), a thioredoxin reductase inhibitor, impedes the proliferation of prostate cancer cells *via* S phase arrest and apoptosis. The use of organoselenium compounds in tumor control has also been demonstrated in five-membered ring systems (**77** and **79**). The efficient tumor growth control by **77** and **79** and the relatively low activity of **78** suggest that at least one C-Se bond is necessary for anti-tumor activity of cyclic selenides as in **78** selenium is bonded to two nitrogen atoms[64].

Liver and gastric mucosal damage: Ebselen (**1**) is found to be an effective inhibitor of galactosamine/endotoxin-induced hepatitis, in which inhibition of LOXs is thought to be involved[65]. When injury was induced by paracetamol, CCl_4, lipopolysaccharide and P*ropionibacterium acnes* and alcohol. In fact, exposure to very high doses of diselenides caused hepatotoxicity in rodents[66]. Gastric mucosa suffers most damage as side effect of all non steroidal anti-inflammatory drugs (NSAIDS). Hence, the fact that organoselenium compounds have no irritant or damaging effect on the gastric mucosa is of huge significance.

Neuroprotection: Ebselen (**1**) has shown promising results with regard to protection against brain damage from permanent focal ischemia, transient focal ischemia[67] and hypoxia/ischemia induced neuronal damage[68]. Ebselen has

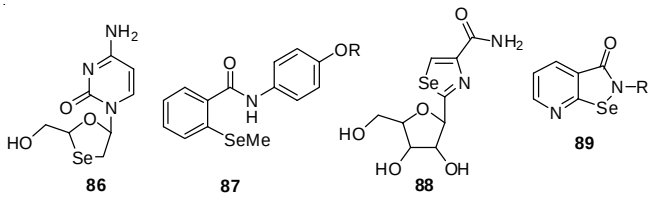


Scheme-V: Chemopreventive synthetic organoselenium compounds

been shown to produce an antioxidant effect in different experimental models of neurotoxicity, in fact, ebselen acts at the redox sensitive NMDA receptor site and reverses dithiothreitol potentiation of NMDA-mediated currents in cultured neurons[69]. Diphenyl diselenide has been established as a neuroprotector agent in a classical model of *in vitro* ischemia[70] and an inductor of facilitation of long-term object recognition memory[71]. Over expression of nitric oxide synthase (iNOS) caused by glucose and oxygen deprivation in rat brain slices was blocked by ebselen and diphenyl diselenide and it was assumed that they inhibited the excessive NO production by iNOS, which occurs after brain ischemia *in vitro*.

Anti-infective agents: Selenazofurin and oxaselenolane nucleoside are selenium containing antivirals, which act as nucleoside synthetase inhibitors **86**[72]. Though it shows a broad spectrum of antiviral activity, unfortunately selanazofurin **87** is highly toxic even at therapeutic concentrations making it an unsuitable therapeutic. *in vitro* Activity against HIV at nano-molecular concentrations has been observed in case of compound **86**. The 7-azabenzisoselenazol-3(2*H*)-ones (**88 Scheme-VI**) substituted at 2-position with phenyl or alkyl groups and the methiodides **89**, were reported to be strong inhibitors of cytopathic activity of herpes simplex type 1 virus (HSV-1) and encephalomyocarditis virus (EMCV). The

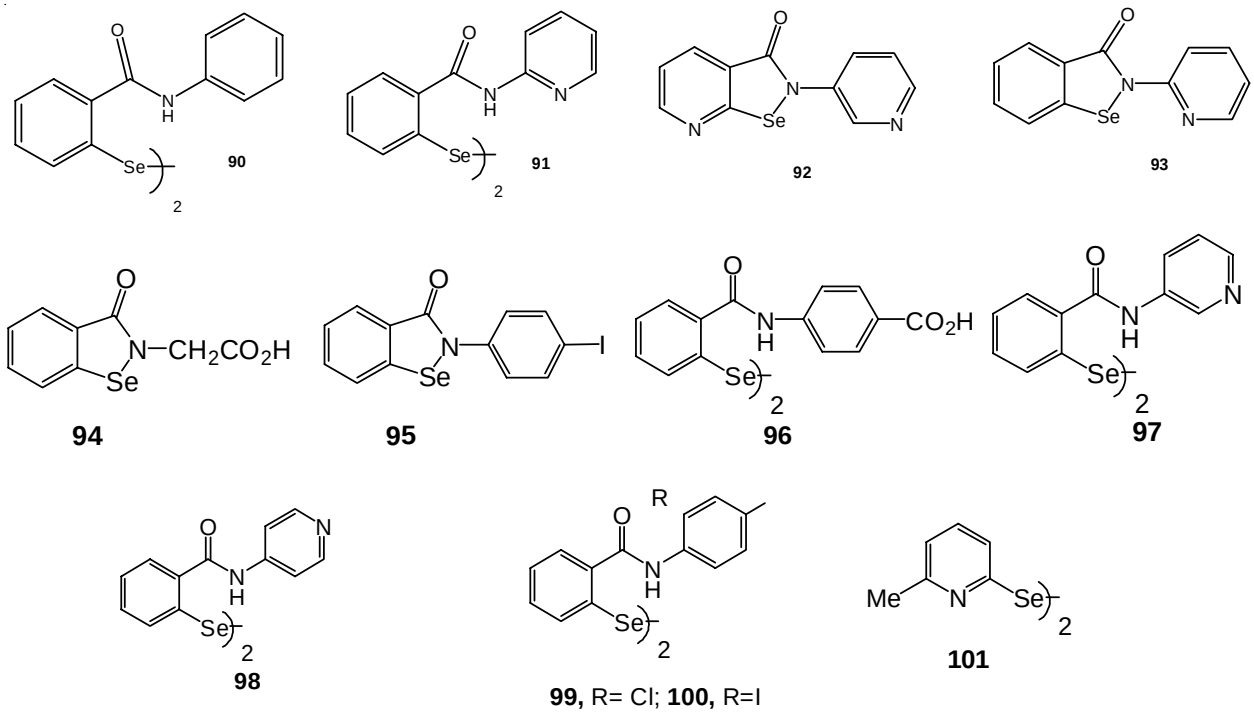
minimal inhibitory concentration (MIC) values were in a range 0.4-6.0 μg/mL which is substantially lower than toxicity value[73] Selenazofurin showed antiviral activity against type I herpes simplex virus, type 3 parainfluenza virus and type 13 rhinovirus was associated with inhibition of guanine nucleotide biosynthesis[74]. The antibacterial activities of ebselen and several other benzisoselenazo-3(2*H*)-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 exhibited strong inhibitory activity against the growth of fungi *Saccharomyces cerevisiae* and *Candida albicans* strains. Several benzisoselenazo-3(2*H*)-ones have been tested *in vitro* against pathogenic bacteria, yeasts and filamentous fungi *Aspergillus niger*, *Penicillum chrysogenum* and *Penicillum citrinum*[75].



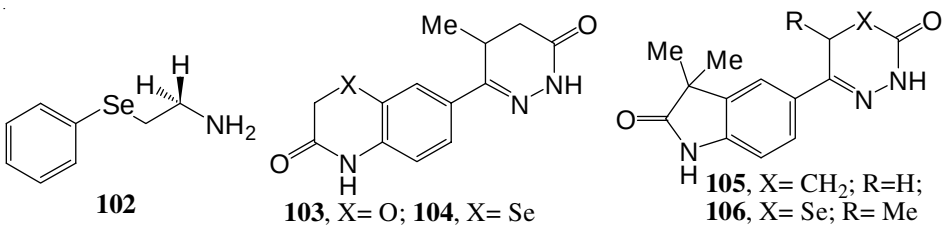
Scheme-VI: Synthetic antiviral organoselenium compounds

Cytokine inducers and immunomodulators: Certain selenocarbazides and inorganic selenium are already known to be potential immunostimulants and inducers of interferon γ (INF-γ) and other cytokines. Apart from these, various organoselenium compounds have been found as effective cytokine inducers[76]. Ebselen and related compounds have been found to act as INF-γ and tumor necrosis factor (TNF) inducers in human peripheral blood leukocytes (PBL). Ebselen and compounds **90**, **91** containing *o*-carbamoyl groups were more effective than the diselenides containing no *ortho* substituent. Cyclic compounds, **23**, **92-95** and diselenides, **96-101** have proved to be potent immunomodulators, most potent being *bis*(2-carbamoyl)phenyl diselenide containing 4-chlorophenyl, **98** and **95**. It has been found that the 2-pyridine derivative **93** can modulate the cytokine production in hyporeactive broncho alveolar leukocytes of asthma patients and thus, is a potential therapeutic agent in asthma[77] (**Scheme-VII**).

Antihypertensive and cardiotonic agents: Variety of Organoselenium compounds have been synthesized that can act as antihypertensive agents as alternate substrate for the key enzyme of catecholamine metabolism, dopamine-α-monooxygenase (DBM)[77,78]. Compound **102**, phenyl-2-aminoethyl selenide, has been found to be an excellent substrate for DBM. Chalcogen analogues of bemoradan (**103**) and indolidan (**105**) have been found to be cardiotonic agents by replacing oxygen atom by Se yielding **104** and **106 (Scheme-VIII)**[79,80].



Scheme-VII: Synthetic organoselenium compounds as Cytokine inducers and Immunomodulators



Scheme-VIII: Organoselenium compounds as antihypertensive and cardiotonic agents

Conclusion

Ebselen and other organoselenium compounds possess therapeutic potential against various diseases and several research groups have reported a large number of synthetic organo selenium compounds for medicinal applications by either modifying the basic structure of ebselen or by incorporating selenium metal in the pharmacophoric structure of the available drug. In many cases, these synthetic organoselenium compounds have proven to be advantageous over available drugs in use. Owing to the significant biological potential of organo-selenium compounds for a plethora of medicinal applications, design and synthesis of organoselenium compounds can be made from the structural features of the compounds of desired activity. We hope that the perspective emphasized in this mini review will direct the attention of synthetic chemists in designing and synthesizing novel organoselenium compounds of therapeutic significance.

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