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Selenium- and Tellurium-Containing Multifunctional Redox Agents as Biochemical Redox Modulators with Selective Cytotoxicity

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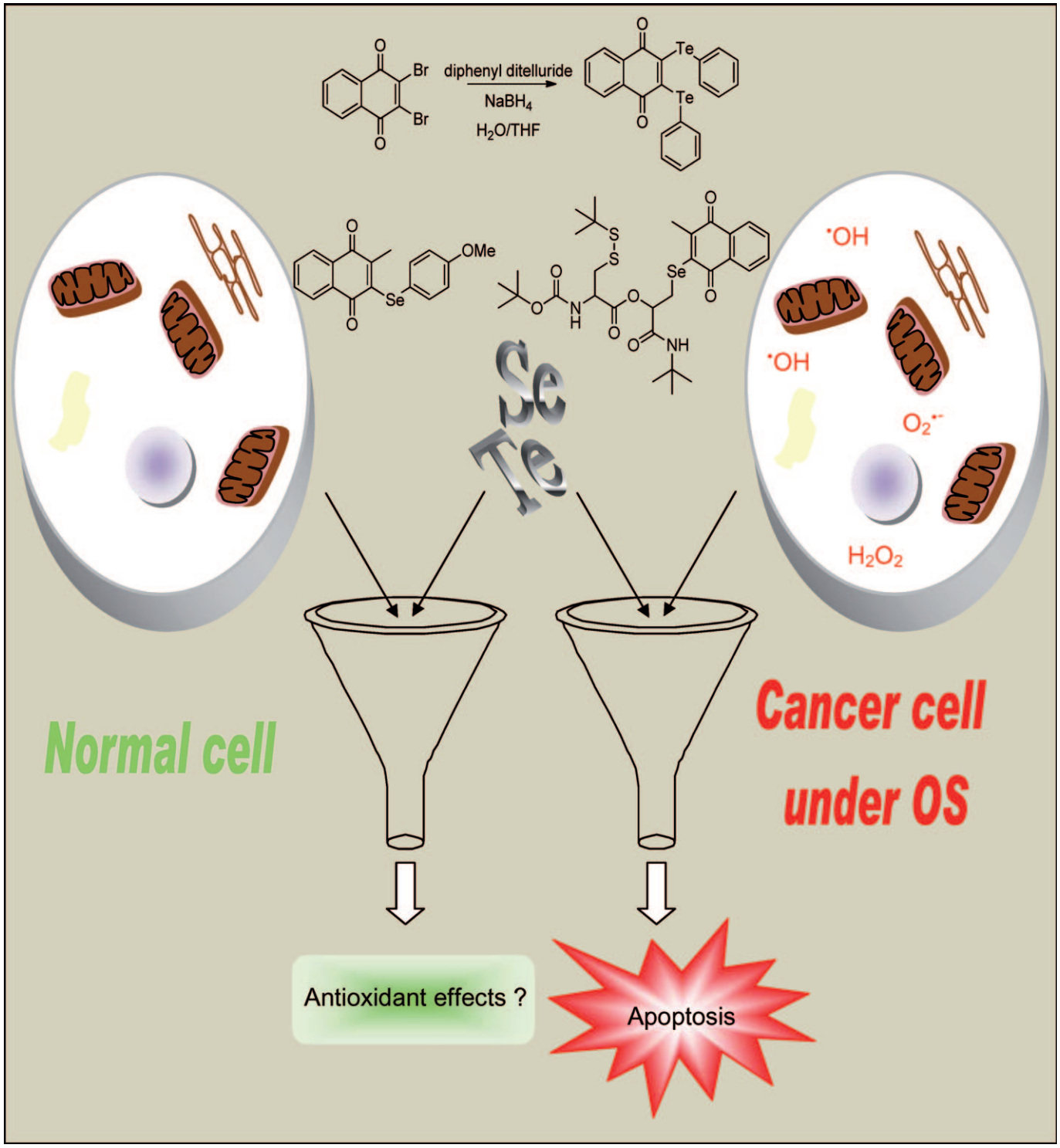


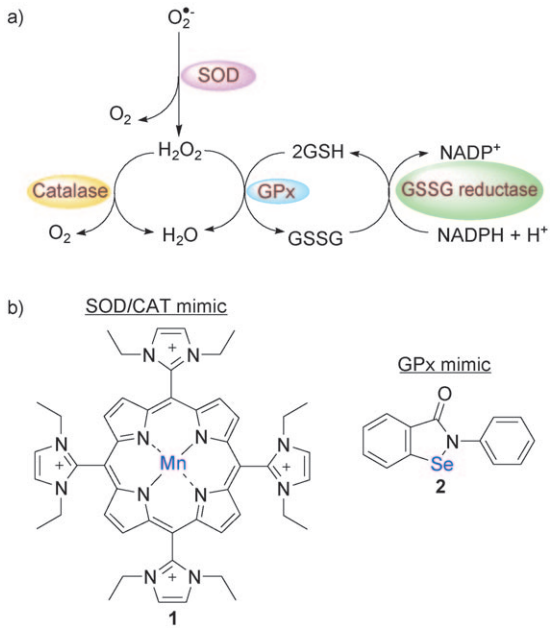
Abstract: Various human diseases, including different types of cancer, are associated with a disturbed intracellular redox balance and oxidative stress (OS). The past decade has witnessed the emergence of redox-modulating compounds able to utilize such pre-existing disturbances in the redox state of sick cells for therapeutic advantage. Selenium- and tellurium-based agents turn the oxidizing redox environment present in certain cancer cells into a lethal cocktail of reactive species that push these cells over a critical redox threshold and ultimately kill them through apoptosis. This kind of toxicity is highly selective: normal, healthy cells remain largely unaffected, since changes to their naturally low levels of oxidizing species produce little effect. To further improve selectivity, multifunctional sensor/effector agents are now required that recognize the biochemical signature of OS in target cells. The synthesis of such compounds provides interesting challenges for chemistry in the future.

Keywords: cancer · multifunctional agents · redox chemistry · selenium · tellurium

Introduction

From oxidative stress to redox signaling: Research during the last three decades has provided increasing evidence that a vast number of human diseases are associated with distinct disturbances in the intracellular redox state. Such pathological changes range from highly reducing environments found in certain hypoxic tumors to the presence of oxidative stress (OS) in various cancer cells and cells associated with inflammatory diseases. OS is characterized by a sharp increase in the intracellular concentration of reactive, oxidizing species, such as reactive oxygen species (ROS, for example, singlet oxygen, H_2O_2, $O_2^{\bullet-}$, and $^{\bullet}OH$ radicals), reactive nitrogen species (RNS, including $NO^{\bullet}$ and peroxynitrite, $ONOO^-$) and free, adventitious metal ions (mostly copper and iron ions). Increases in reactive species are often combined with a loss of antioxidant defense, such as low levels of reduced glutathione (GSH) and diminished antioxidant enzyme activity. Table 1 provides a current, incomplete, and still expanding list of human ailments associated with a disturbed redox balance, among them various types of cancer, neurodegenerative diseases, auto-inflammatory diseases, rheumatoid arthritis, bacterial and viral infections, diabetes mellitus, and glaucoma.[1] Notably, many of these illnesses are associated with old age, which may be related to a certain natural loss of antioxidant defense capacity in older organisms. For instance, we now know that there is a connection between loss of antioxidant capacity, raised ROS levels, DNA damage, and the development of cancer. Such diseases are therefore likely to increase in importance as our societies continue to age.[2]

These discoveries have fuelled the search for natural chemopreventative products and have opened up a multibillion Euro market for antioxidants, especially vitamin supplements. Since enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), remove oxidants by catalysis, that is, are particularly effective as antioxidants, a wide range of agents mimicking these enzymes has been synthesized over the years and tested with mixed success in biological systems (Scheme 1).[3–5]



Scheme 1. The detoxification of ROS inside the human cell relies on enzymes such as SOD, CAT, and GPx (a). Mimics of these enzymes have been synthesized (b) and tested extensively for antioxidant activity in biological systems.

More recently, however, it has become apparent that the early, rather simplistic notion of OS as the "bad guy" damaging human cells does not reflect the true complexity of intracellular redox signaling: Even in situations not directly associated with human host defense (which requires the generation of ROS), human cells rely heavily on beneficial concentrations of oxidants, such as H_2O_2.[6] Their intentional removal, for instance, by excessive use of antioxidants (e.g., vitamin C), may actually be detrimental to human health.[7] This "antioxidant paradox" has been highlighted by studies

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Table 1. List of human ailments that, to date, have been associated with a disturbed redox balance.

Vascular diseases	Immune diseases	Diseases of the nervous system	Pulmonary diseases	Others organ diseases
atherosclerosis	Crohn's disease	Alzheimer's disease	acute chest syndrome of sickle cell disease	alcoholic liver disease
coronary artery disease	HIV infections	amyotrophic lateral sclerosis	adult (acute) respiratory distress syndrome	cataract genesis
hyperhomocysteinemia	primary biliary cirrhosis	Creutzfeldt–Jakob disease	asthma	chronic hepatitis C
hyperlipidemia	reactive arthritis	mild cognitive impairment	bronchopulmonary dysplasia	chronic kidney disease
ischemia/reperfusion injury	systemic lupus erythematosus	multiple sclerosis	asbestosis	chronic renal failure
brain ischemia	systemic sclerosis (scleroderma)	Parkinson's disease	chronic obstructive pulmonary disease	cutaneous leishmaniasis
diabetes mellitus		Friedreich's ataxia	idiopathic pulmonary fibrosis	Down's syndrome
myocardial infarction		Huntington's disease	interstitial lung disease	obesity
myocardial inflammation		Zellweger's syndrome	cystic fibrosis	osteoarthritis
pre-eclampsia			pulmonary hypertension	osteoporosis
heart failure			respiratory distress disease	pancreatitis
hypercholesterolemia				renal cell carcinoma
sickle cell disease				retinopathy of prematurity
spherocytosis				rheumatoid arthritis
stroke				Werner's syndrome
unstable angina				

in mutant mice expressing elevated levels of (antioxidant) GPx: These mice are sick—they suffer from a diabetes-like pathology due to the decreased impact of insulin.[8] Other studies have shown that supplementation with (antioxidant) vitamin C or E also prevents some of the beneficial effects of exercise, such as adaption to stress.[9,10] These adaptive, and highly beneficial, processes are apparently induced by mildly elevated levels of H_2O_2, and are prevented by antioxidants that remove H_2O_2.

The notion of ROS as outright damaging chemical species is therefore giving way to a more differentiated view, which considers ROS-based, concentration-dependent cellular redox signaling, regulation, and control.[11] In this context, a publication by Schafer and Buettner in 2001 has highlighted the rather complex correlation that exists between the intracellular glutathione redox state on the one hand, and cell proliferation, apoptosis, and necrosis on the other (Figure 1).[12] In essence, the electrochemical potential E reflects the relative concentrations of oxidized and reduced cellular species, such as the glutathione disulfide (GSSG)/glutathione (GSH) redox pair. The ratio between GSSG and GSH in turn influences the extent of S-glutathiolation of various proteins and enzymes, the activity of which is regulated by glutathiolation/deglutathiolation processes. Considering that numerous key regulatory enzymes, including caspases, Bcl-2 proteins, and various kinases, contain active-site cysteine residues, that is, are prone to redox regulation by glutathiolation/deglutathiolation, the impact of the GSSG/GSH redox state on many cellular processes becomes apparent.

It is, of course, too simplistic to describe cellular redox signaling solely as a result of one particular E value: Kinetic aspects also play a major role. Not all enzymes are able to react with GSSG, even if present at high concentrations. Steric hindrance may, for instance, prevent active-site cysteine residues from being modified. Furthermore, the electrochemical potential E only applies to one particular redox pair in a state of equilibrium, while the cytosol of the cell is far from an overall equilibrium state and contains many individual redox systems, each with a specific, continuously changing E value. Nonetheless, this scheme explains why ROS, such as H_2O_2, may control essential cellular functions and even stimulate cell growth at low concentrations, while

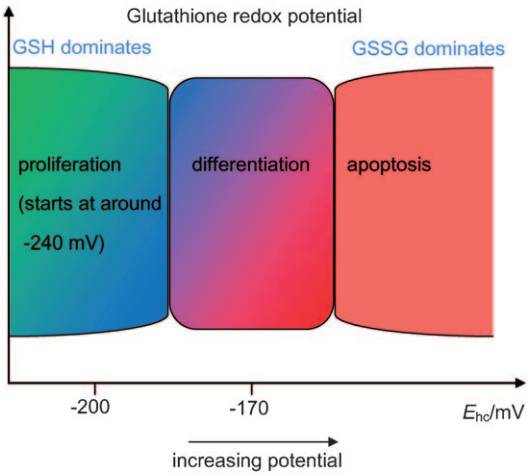


Figure 1. Postulated correlation between the ratio of GSSG/GSH and the intracellular redox potential E on the one hand, and cell proliferation, differentiation, and apoptosis on the other. Although this cartoon may appear as rather simplistic, recent research has provided considerable evidence that the GSSG/GSH ratio (and indeed related RSSR/RSH ratios) in the cell determine the extent of S-thiolation and hence activity of numerous key cellular proteins and enzymes (including various Bcl-2 proteins, caspases, kinases), hence formally linking E to a wide range of cellular signaling pathways. These pathways also control proliferation, differentiation, and apoptosis.

inducing apoptosis or turning outright toxic (necrosis) at elevated levels, for instance in form of OS.

Such a more differentiated look at ROS not only refines the older notion of ROS as outright toxic, but also explains many observations related to the beneficial effects of H_2O_2 that have been puzzling scientists in the past.[13] At the same time, the indiscriminate hunt for more, and more effective, natural and artificial antioxidants, which indeed has provided some very elegant chemistry over the years, is slowly turning into a more considerate search for redox modulators that may interfere with redox signaling in a highly specific and hence selective manner. We will now discuss the development of suitable redox-modulating sensor/effector agents, which brings together the latest developments from biochemistry and synthetic chemistry, including multicomponent reactions and little-known selenium and tellurium chemistry.

Discussion

Modulators of the intracellular redox balance: The idea of exploiting the presence of disturbed redox balances for therapeutic purposes is not new.[14] The concept of bioreductive drugs, for instance, is based on the fact that hypoxic areas of solid tumors, which are deprived of normal oxygen supplementation, develop an unusual intracellular redox environment rich in reducing enzymes, such as DT-diaphorase and NADPH-cytochrome P-450 reductase (DT = di- and triphosphopyridine nucleotide, NADPH = nicotinamide adenine dinucleotide phosphate).[14–16] These enzymes may be used to activate anticancer drugs through enzymatic reduction, such as mitomycin C (MMC) and a range of chemically related agents. At the other end of the redox scale, there have been various attempts to exploit OS existing in sick cells for therapeutic purposes (Figure 2). Within the context of cancer research, such redox modulation relies on the fact that many cancer cells are naturally under OS, and when compared to healthy cells, their ROS levels are considerably closer to the critical redox threshold at which apoptosis is induced. By raising ROS levels in such cells even further, apoptosis may be induced rather selectively, though a similar increase in ROS levels is also triggered in healthy cells, yet without the same dramatic consequences. Straightforward examples of compounds able to raise ROS levels include As_2O_3 and ROS-generating quinones.[17–19] Apart from artificially raising ROS levels by ROS generation, similar effects may be obtained by lowering the cell's antioxidant defense. Inhibitors of human Cu,Zn-SOD, such as 2-methoxyestradiol (2-ME), for instance, prevent the intracellular conversion of $O_2^{\bullet-}$ to H_2O_2, which is detoxified further by CAT, GPx, or peroxiredoxins.[20] The intracellular build-up of $O_2^{\bullet-}$ triggered by such SOD inhibitors leads to an oxidizing redox environment that induces apoptotic cell death in human leukemia cells.[21] This event is selective for cancer cells that are naturally rich in ROS: While 2-ME is also active in normal cells, the resulting increases in ROS levels are rather modest and do not induce apoptosis.

Whereas these approaches, by considering the redox threshold required for induction of apoptotic cell death, rely on pre-existing differences in ROS levels between diseased and normal cells, ROS generators and inhibitors of antioxidant proteins add an additional ROS burden without really discriminating directly between normal and sick cells (Figure 2, scenarios **A**, **B**, and **C**). There is, however, a powerful alternative: catalytic molecules that employ ROS as their substrates may not only raise ROS levels, they may also do so rather selectively in cells rich in ROS, without exhibiting the same chemistry in normal cells. This fine difference between ROS generators on the one hand, and ROS

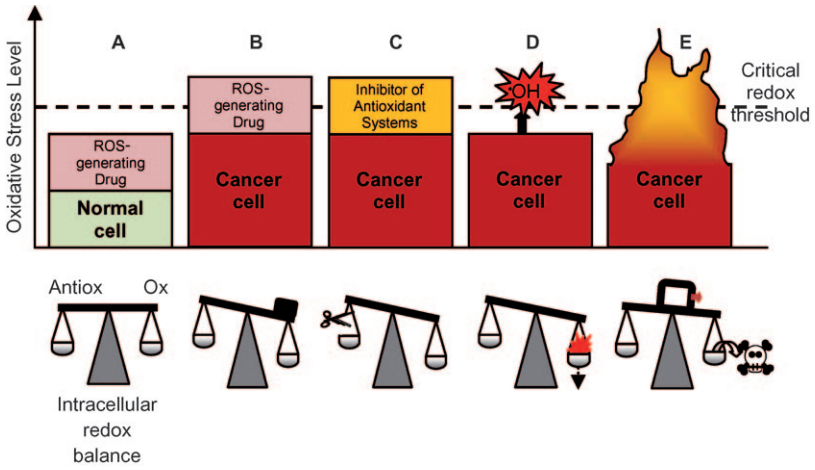


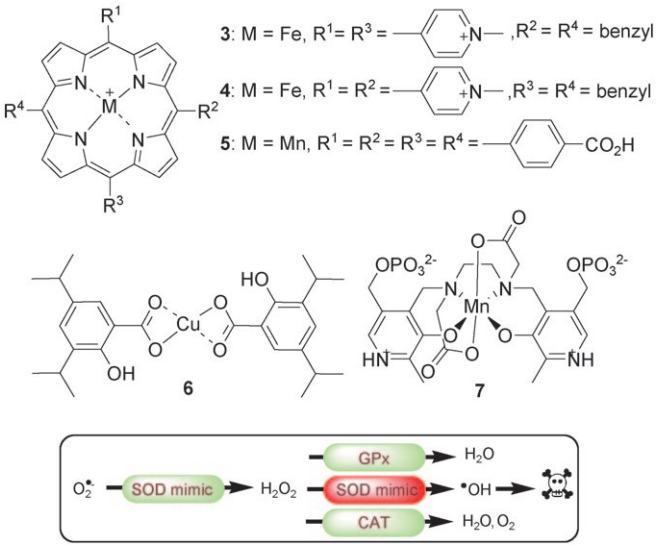
Figure 2. Models explaining how redox modulation of a pre-existing intracellular redox state may result in selective cytotoxicity against cancer cells rich in ROS. While drugs may increase OS in normal (scenario **A**) and cancer cells, only cancer cells, which are already closer to the critical redox threshold for induction of apoptosis, are killed (scenarios **B** and **C**). The increase of OS may be caused either by ROS-generating agents or by inhibitors of antioxidant enzymes. Such approaches are somewhat crude, since they do not use the presence of pre-existing ROS to their own advantage. In contrast, catalytic agents, such as certain SOD mimics, may be able to convert pre-existing ROS in cancer cells into highly damaging radicals (scenario **D**). Other catalysts, such as GPx mimics, do not change the pre-existing redox balance or ROS composition, but facilitate the reaction of ROS—the levels of which are increased in cancer cells—with redox-sensitive pivotal proteins and enzymes, the rapid oxidation/modification of which subsequently triggers apoptotic processes in the cancer cells (scenario **E**). Please note that this is a preliminary model, and issues such as differences in redox thresholds between normal and cancer cells or antioxidant activities associated with certain compounds in vitro require further exploration. (Antiox = antioxidants; Ox = oxidants.)

users on the other, has significant implications for selective drug design. This leads to the area of sensor/effector agents and to metallo-organic, selenium, and tellurium chemistry.

Towards intelligent sensor/effector molecules: We have recently promoted the term sensor/effector molecule to denote agents able to recognize a particular cellular imbalance and to respond accordingly.[22] Here, catalytic agents are particularly suitable: The presence of substrate in the cell triggers the catalytic process, which is highly efficient, yet only occurs if and as long as the substrate is present. Elevated intracellular levels of $O_2^{\bullet-}$ or H_2O_2 in certain cancer cells, for instance, may be used by the catalyst to generate a lethal cocktail of ROS or to oxidize key proteins. Such events, in turn, may induce apoptosis, the preferred mode of cancer cell death in therapy.[23] Healthy cells naturally low in ROS are affected to a lesser extent: Although the catalyst is also active in these cells, the limited amount of available substrate prevents the catalyst from causing any major damage. Sensor/effector molecules may therefore show little toxicity and side effects on their own—they may even act as antioxidants in some cells exposed to low levels of OS. Although the concept of sensor/effector molecules is therefore highly attractive, one must emphasize, however, that it is still rather speculative at this time and further studies are required to provide more concrete evidence for (or against) these notions.

In principle, we can distinguish two classes of catalytic sensor/effector agents. On the one side, there are compounds able to convert less reactive and damaging ROS, such as $O_2^{\bullet-}$, to more damaging species, such as the highly aggressive hydroxyl ($^{\bullet}OH$) radical (Figure 2, scenario **D**). Such catalysts, which include various SOD mimics, rely on pre-existing ROS in cancer cells and generate a different composition of ROS. On the other side, we find molecules able to speed up the reaction of ROS with redox-sensitive proteins and enzymes. While these compounds, which include GPx mimics, also rely on pre-existing ROS, they do not generate any new ROS, but have a truly kinetic effect (Figure 2, scenario **E**).

Whereas the notion of sensor/effector agents is based on some rather straightforward principles, the search for agents fulfilling the above criteria is rather complicated. In the early 2000s, Kawakami and co-workers at Tokyo Metropolitan University reported the apparently selective activity of porphyrin-containing Fe–SOD mimics against Walker 256 and H-4-II-E cancer cells in a rat model (for chemical structures see Scheme 2).[24] While the cancer cells were killed with high efficiency, FR and BRL-3A control cells were less affected. At around the same time, the group of Batteux at Paris Descartes University investigated a wider range of SOD mimics that were subsequently tested in CT26 tumor cells implanted in mice.[25] These experiments demonstrated that catalytic redox agents, in combination with certain conventional anticancer agents (e.g., oxaliplatine), were able to attack cancer cells very efficiently, even when employed at rather low concentrations. At the time, it was thought that



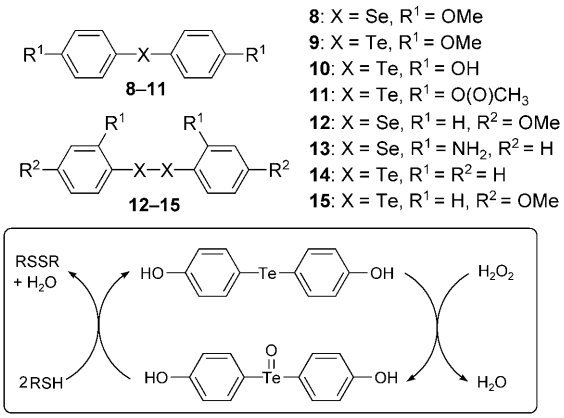
Scheme 2. Compounds employed by the groups of Kawakami and Batteux to target cancer cells. These compounds structurally resemble SOD mimics, yet develop pronounced pro-oxidant, cytotoxic effects in the presence of H_2O_2, probably due to their ability to catalytically generate $^{\bullet}OH$ radicals (inset).

such compounds would convert $O_2^{\bullet-}$ and/or H_2O_2 to $^{\bullet}OH$, which would then react with a range of essential biomolecules, damage the cell, and induce cell death. [Although such compounds were originally developed as SOD mimics, their (bio)chemical reactivity is very different from that of the parent enzyme: SOD converts $O_2^{\bullet-}$ to H_2O_2 and O_2, but does not produce $^{\bullet}OH$ radicals, although certain radical-generating SOD mutations may have been identified in familial amyotrophic lateral sclerosis (FALS), which could actually cause severe cell damage in the brain.][26]

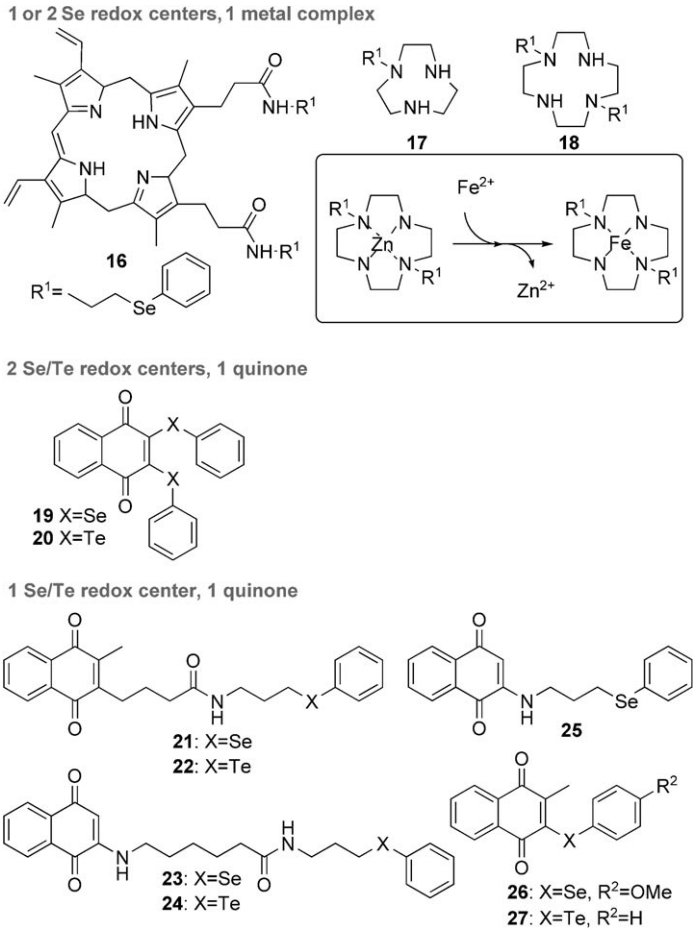
While SOD is an antioxidant enzyme that converts $O_2^{\bullet-}$ to H_2O_2 and O_2, its suspected mimics also recognize $O_2^{\bullet-}$ and H_2O_2 as substrates, yet turn them into very different, lethal products.

A similar difference in substrate specificity between parent enzyme on the one hand and its mimics on the other is also found in the case of Se- and Te-based mimics of human GPx (Scheme 3).[27,28] GPx contains an active-site selenocysteine residue and catalyzes the reduction of H_2O_2 and certain peroxides to water (alcohol) in the presence of a thiol substrate that is subsequently oxidized and used up. Whereas GPx relies on sacrificial GSH as almost the sole substrate, certain GPx mimics are less specific: these compounds also oxidize redox-sensitive thiol groups in proteins and enzymes (Scheme 3, inset). Indiscriminate thiol oxidation catalysis is, however, highly detrimental to the cell, which explains the high toxicity of such Se- and Te-based compounds in the presence of significantly elevated concentrations of H_2O_2.

In the context of anticancer research, selenium is not a bad choice. The toxicity of certain selenium compounds, such as selenite (SeO_3^{2-}) and selenodiglutathione



Scheme 3. Se and Te agents employed to target cells under H_2O_2-induced OS. The compounds shown belong to the first generation of agents tested by us, and in many respects still resemble the typical features associated with GPx mimics. Unlike GPx, however, which almost exclusively consumes sacrificial GSH, these compounds are less specific and prey on various cysteine thiols (RSH), including cysteine residues in proteins and enzymes (inset). As a consequence, some of these compounds may show certain antioxidant properties in commonly used in vitro assays, yet are actually cytotoxic in cell-based assays.



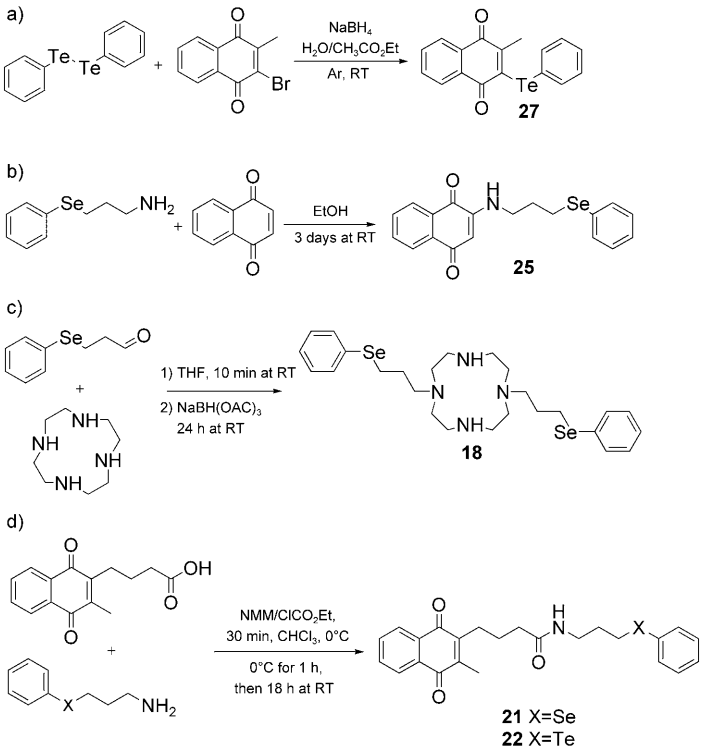
Scheme 4. A selection of multifunctional agents that have been designed to recognize the biochemical signature of OS in cells. These compounds are able to modulate the intracellular redox environment in various ways, including radical generation (via the quinone moiety), thiol oxidation (via the chalcogen moiety), and the sequestering of metal ions into chelate ring systems, a process that may result in the formation of iron- or copper-containing sites for catalytic $^{\bullet}OH$ radical formation.

(GSSeSG), against cancer cells has been known for a number of years.[29] Inside the cell, these Se compounds seem to be transformed into active Se species, which in turn generate ROS catalytically, probably by reducing O_2 to $O_2^{\bullet-}$ and certain follow-on products in the presence of GSH. It should be pointed out that in contrast to sensor/effector agents, which use pre-existing ROS as substrate, this kind of catalysis employs (pre-existing) O_2, which is omnipresent, and does not in itself endow selectivity. The effects of SeO_3^{2-} and GSSeSG, hence, rather resemble the ones of other ROS-generating compounds, such as quinones and As_2O_3 (see Figure 2), yet may be particularly efficient due to catalysis. In any case, the therapeutic potential of selenium agents has not been fully explored in the context of cancer research. [Among the various Se compounds studied, only the GPx mimic ebselen has researched Phase III clinical trials in Japan, yet as an antioxidant in the context of stroke and not as anticancer agent.][30]

We have tested our first Se- and Te-based catalysts able to recognize and respond to elevated H_2O_2 levels in cancer cells in 2001 (Scheme 3). Compounds such as 4,4'-dihydroxydiphenylditelluride **10** indeed exhibited some selectivity for the cells under (externally induced) H_2O_2 stress, with lower activity in cells devoid of external H_2O_2. While these experiments may well be seen as an early proof of concept, they did employ rather high concentrations of Se and Te compounds. Since a disturbed redox balance is not just due to one chemical species, such as H_2O_2, but is the result of a combination of various ROS, RNS, metal ions, and deficiencies in antioxidant defenses, tailor-made compounds combining more than one redox center in the molecule were considered to increase efficiency and selectivity (Scheme 4).[31–34] This approach proved to be highly successful: By combining a ROS-generating moiety with a GPx-like catalytic center, the resulting bifunctional ROS-generating/ROS-using agents were considerably more active in cell culture (compared with our first generation Se and Te catalysts) and, for the first time, could be employed effectively in sub-micromolar concentrations.

The desire to increase the selectivity for cancer cells under OS even further has recently stimulated the synthesis of considerably more complicated multifunctional agents, which are tailored according to the biochemical redox signature of cancer cells and often combine three or even more functionalities (redox centers, metal binding sites) in one molecule.

Coupling of building blocks and multicomponent reactions: The synthesis of such multifunctional compounds can follow different avenues (Schemes 5 and 6). It is possible, for instance, to start with one particular scaffold molecule and to add-on additional biochemically interesting functions. While

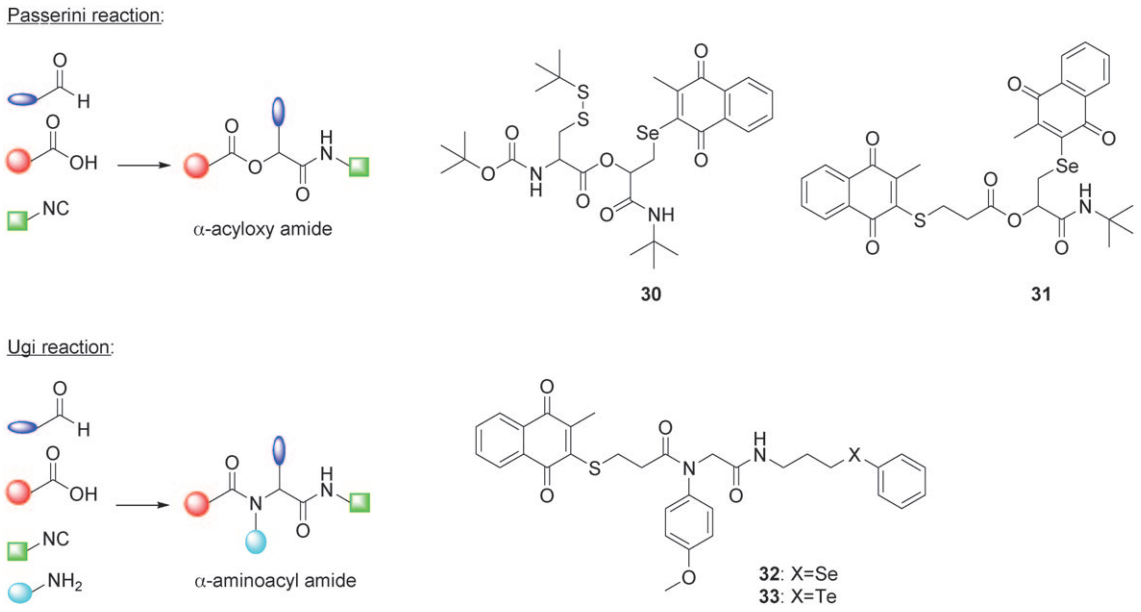


Scheme 5. Synthesis of multifunctional agents by nucleophilic substitution by a redox-active chalcogen moiety at a quinone core structure (a), by aminoalkylation proceeding through nucleophilic attack of the amine-based nucleophile at the quinone (b), by reductive amination involving the reaction of amine and aldehyde to imine with subsequent reduction to amine (c), and by amide coupling involving the reaction of amine and carboxylic acid (peptide coupling) (d).

this approach appears to be straightforward at first sight, it is often hampered by the high reactivity and/or instability of some of the desired features. It is rather difficult, for example, to modify selenium and tellurium agents without risking decomposition.

There is, however, a rather promising alternative, which involves the initial synthesis of different building blocks, each containing one biochemically interesting functionality (such as a Te atom, redox center, or metal binding site). These building blocks are coupled together in a final assembly step (e.g., amide coupling, and multicomponent Passerini and Ugi reactions).[35] As long as the individual blocks are chemically stable, and the final coupling proceeds under mild conditions, this approach turns out to be extremely fruitful and has already been used to generate a wide range of different selenium and tellurium compounds (Scheme 6). Some of these molecules feature three or even four biochemically interesting sites in one molecule.

Compared with more traditional synthetic avenues in Se and Te chemistry, this building-block assembly approach has various advantages. First of all, it is possible to synthesize a wide range of highly functionalized Se and Te compounds in good yields and with comparable ease. Second, the use of different building blocks, such as various amines, aldehydes, isonitriles, and carboxylic acids, allows an extensive mix and match of individual blocks carrying functions of interest. Once an arsenal of suitable building blocks has been acquired, it is possible to select the desired blocks from this arsenal and to assemble them into highly diverse molecules. Depending on the target at hand, one may generate molecules with various redox sites, combine redox and metal binding sites, or include additional functionalities, for in-



Scheme 6. Synthesis of multifunctional agents by multicomponent Passerini and Ugi reactions. These methods rely on preformed building blocks and employ a final assembly step. The Passerini reaction is a three-component reaction combining an acid, aldehyde, and isonitrile to form an α-acyloxy amide, whereas the Ugi reaction is a four-component reaction (acid, aldehyde, isonitrile, and amine) leading to an α-aminoacyl amide.

stance, sites for interactions with specific enzymes or receptors.

Indeed, some of the compounds generated by the mix and match approach have already shown distinct biological activities. A combination of Se and Te centers with quinones (**21** and **22**) is active against *Plasmodium falciparum*, the microorganism responsible for malaria, which naturally possesses a weak antioxidant defense. Other multifunctional agents combining a redox center with a metal binding site are effective against parasitic fungi, such as the dermatophyte *Tricophyton rubrum*, which is hit simultaneously by ROS generation and metal-ion deprivation. In this case, lack of access to essential metal ions not only hampers fungal growth, but also weakens the antioxidant defense of the fungus against ROS, since many of its antioxidant enzymes are metal dependent.

Most exciting, of course, are compounds with selective activity against cancer cells.[34] So far, several of the multifunctional agents shown in Schemes 4, 5, and 6 have been screened at the National Cancer Institute (NCI) of the National Institute of Health (NIH) in Bethesda, MD (USA), and studied in more detail in cell culture, human patient blood, and mouse models. Based on these studies, our latest results confirm that compounds such as **20**, **24**, **30**, and **31** (with **30** and **31** combining three and four redox sites in one molecule, respectively), fulfill the requirements of sensor/effector agents. In cell culture as well as in the blood of chronic lymphocytic leukemia (CLL) patients, these compounds respond to elevated, pre-existing levels of ROS by further increasing OS. Redox-controlled, often caspase-dependent apoptotic processes are subsequently initiated that ultimately lead to the death of the cancer cells. In sharp contrast, healthy cells with normal levels of ROS (such as NIH 3T3 cells, peripheral blood mononuclear cells (PBMC) from healthy patients, and even the remaining healthy B cells obtained from the same CLL patient donating the cancerous B cells) are less affected. The quinone–Te compounds studied so far do not raise ROS levels in healthy cells significantly, and the resulting ROS levels, albeit somewhat higher than in untreated cells, are not sufficient to trigger apoptosis. In essence, normal healthy cells survive in the presence of **20**, whereas cancer cells often do not.

Summary and Outlook

Initial studies on multifunctional Se and Te agents have corroborated the concept of redox-modulating catalysts as potentially fairly selective anticancer agents. Nonetheless, considerably more and more detailed studies are required to ultimately confirm the notion of selective sensor/effector molecules. In the future, this emerging field therefore needs to expand in chemistry, biochemistry, metabolic studies, and in its biological/medical applications. As far as chemistry is concerned, innovative molecules designed to recognize the biochemical target signature with great precision have to be synthesized. Although compounds based on chalcogens have turned out to be particularly useful, this chemistry does not have to be restricted to selenium and tellurium.

At the same time, the biochemical pathways triggered by these agents need to be studied in more detail. While a connection between the redox catalysts, intracellular redox control, and apoptosis is emerging, many questions still remain. To begin with, the initial target of such redox modulators is still unknown. Possible candidates include redox-sensitive, cysteine-containing Bcl proteins, which control apoptosis at an early stage, yet certain caspases, which execute apoptotic mechanisms further downstream, are also redox sensitive. Then again, the redox modulators may not just hit one specific protein target, but cause a more general shift in intracellular redox state, which would result in a widespread modification of proteins and enzymes, for instance in form of S-glutathiolation (see also Figure 1). As an alternative to simple ROS generation or ROS usage, some of the tellurium agents may modulate cellular processes by inhibiting key enzymes, such as the antioxidant enzyme thioredoxin reductase, a process that subsequently would also result in increased OS.[5]

A deeper understanding of such underlying biochemical processes may ultimately pave the way for a therapeutic use of these agents. Here, cancer cells with a disturbed redox

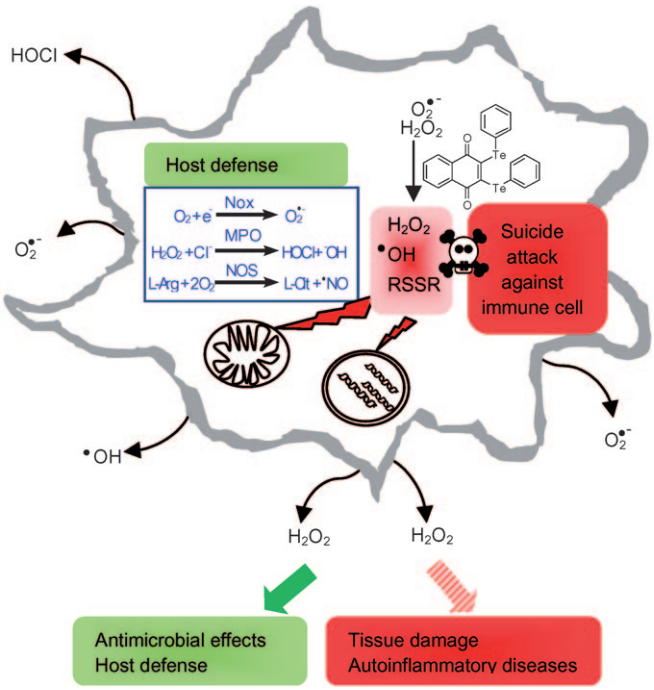


Figure 3. Future targets for sensor/effector agents may include auto-inflammatory diseases, such as RA. This disorder is characterized by permanently activated immune cells that locally generate massive amounts of ROS. Rather than fighting those ROS with the help of antioxidants, which is often a rather futile enterprise, one may consider the use of pro-oxidant catalysts that use ROS generated by out-of-control immune cells to generate an even more lethal mixture of ROS near or inside these cells and hence kill them rather selectively. Once the activated immune cells have been destroyed, the hope is that the inflammation may subside. (Nox = NADPH oxidases; MPO = myeloperoxidase; NOS = nitric oxide synthases.)

balance may be the most prominent, but by no means the only targets. Another interesting area with potential applications relates to inflammatory diseases, such as rheumatoid arthritis (RA). While antioxidants, such as *N*-acetylcysteine,[36] are frequently considered in the treatment of such illnesses, pro-oxidants paradoxically could hold the key to the treatment of some of these disorders: RA, for instance, is characterized by ROS-producing, out-of-control immune cells, including neutrophils and macrophages, some of which have even become unresponsive to apoptotic stimuli.[37] These cells produce extraordinarily high concentrations of ROS. Any Se or Te catalyst placed near or even inside those cells could theoretically trigger a massive, yet localized, oxidative burst, which may selectively destroy the most damaging, over-active immune cells in a kind of self-inflicted suicide attack (Figure 3).

With many of these questions still remaining, and the search for selective therapeutic agents expanding at a breathtaking pace, extraordinary joint research opportunities exist for chemists, pharmacists, biochemists, and cell biologists in the near and medium-term future.

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